(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 May 2004 (21.05.2004)

PCT

(10) International Publication Number
WO 2004/041157 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US2003/029167

(22) International Filing Date: 15 September 2003 (15.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/410,839 13 September 2002 (13.09.2002) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/410,839 (CIP)
Filed on 13 September 2002 (13.09.2002)

(71) Applicant (*for all designated States except US*): **CHIRON CORPORATION** [US/US]; 4560 Horton Street, Emeryville, CA 94608-2916 (US).

(72) Inventor; and
(75) Inventor/Applicant (*for US only*): **RAPPUOLI, Rino** [IT/IT]; Chiron Corporation, P.O. Box 8097, Emeryville, CA 94662-8097 (US).

(74) Agents: **HALE, Rebecca, M.** et al.; Chiron Corporation, Intellectual Property-R338, P.O. Box 8097, Emeryville, CA 94662-8097 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/041157 A2

(54) **Title:** GROUP B STREPTOCOCCUS VACCINE

(57) **Abstract:** This application relates to improved Group B Streptococcus ("GBS") saccharide-based vaccines comprising combinations of GBS polysaccharides with polypeptide antigens, and *vice versa*, such that the polypeptide and the saccharide each contribute to the immunological response in a recipient. The combination is particularly advantageous where the saccharide and polypeptide are from different GBS serotypes. The combined antigens may be present as a simple combination where separate saccharide and polypeptide antigens are administered together, or they may be present as a conjugated combination, where the saccharide and polypeptide antigens are covalently linked to each other. Preferably, the immunogenic compositions of the invention comprise a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected form GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

GROUP B STREPTOCOCCUS VACCINE

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/410,839, filed September 13, 2002, which application is incorporated herein by reference in its entirety.

TECHNICAL FIELD

This invention relates to polysaccharides from the bacteria *Streptococcus agalactiae* (GBS) and to their use in immunisation.

BACKGROUND ART

Once thought to infect only cows, the Gram-positive bacterium *Streptococcus agalactiae* (or "group B streptococcus", abbreviated to "GBS" (Ref. 1) is now known to cause serious disease, bacteremia and meningitis, in immunocompromised individuals and in neonates. There are two types of neonatal infection. The first (early onset, usually within 5 days of birth) is manifested by bacteremia and pneumonia. It is contracted vertically as a baby passes through the birth canal. GBS colonises the vagina of about 25% of young women, and approximately 1% of infants born via a vaginal birth to colonised mothers will become infected. Mortality is between 50-70%. The second is a meningitis that occurs 10 to 60 days after birth. If pregnant women are vaccinated with type III capsule so that the infants are passively immunised, the incidence of the late onset meningitis is reduced but is not entirely eliminated.

The "B" in "GBS" refers to the Lancefield classification, which is based on the antigenicity of a carbohydrate which is soluble in dilute acid and called the C carbohydrate. Lancefield identified 13 types of C carbohydrate, designated A to O, that could be serologically differentiated. The organisms that most commonly infect humans are found in groups A, B, D, and G. Within group B, strains can be divided into at least 9 serotypes (Ia, Ib, Ia/c, II, III, IV, V, VI, VII and VIII) based on the structure of their polysaccharide capsule. In the past, serotypes Ia, Ib, II, and III were equally prevalent in normal vaginal carriage and early onset sepsis in newborns. Type V GBS has emerged as an important cause of GBS infection in the USA, however, and strains of types VI and VIII have become prevalent among Japanese women.

The genome sequence of a serotype V strain 2603 V/R has been published (Ref. 2) and various polypeptides for use a vaccine antigens have been identified (Ref. 3). The vaccines currently in clinical trials, however, are based on polysaccharide antigens. These suffer from serotype-specificity and poor immunogenicity, and so there is a need for effective vaccines against *S.agalactiae* infection.

It is an object of the invention to provide further and improved GBS vaccines.

DISCLOSURE OF THE INVENTION

The inventors have realised that saccharide-based vaccines can be improved by using them in combination with polypeptide antigens, and *vice versa*, such that the polypeptide and the saccharide each contribute to the immunological response in a recipient. The combination is particularly advantageous where the saccharide and polypeptide are from different GBS serotypes.

The combined antigens may be present as a simple combination where separate saccharide and polypeptide antigens are administered together, or they may be present as a conjugated combination, where the saccharide and polypeptide antigens are covalently linked to each other.

Thus the invention provides an immunogenic composition comprising (i) one or more GBS polypeptide antigens and (ii) one or more GBS saccharide antigens. The polypeptide and the polysaccharide may advantageously be covalently linked to each other to form a conjugate.

Between them, the combined polypeptide and saccharide antigens preferably cover two or more GBS serotypes (*e.g.* 2, 3, 4, 5, 6, 7, 8 or more serotypes). The serotypes of the polypeptide and saccharide antigens may or may not overlap. For example, the polypeptide might protect against serogroup II or V, while the saccharide protects against either serogroups Ia, Ib, or III. Preferred combinations protect against the following groups of serotypes: (1) serotypes Ia and Ib, (2) serotypes Ia and II, (3) serotypes Ia and III, (4) serotypes Ia and IV, (5) serotypes Ia and V, (6) serotypes Ia and VI, (7) serotypes Ia and VII, (8) serotypes Ia and VIII, (9) serotypes Ib and II, (10) serotypes Ib and III, (11) serotypes Ib and IV, (12) serotypes Ib and V, (13) serotypes Ib and VI, (14) serotypes Ib and VII, (15) serotypes Ib and VIII, 16) serotypes II and III, (17) serotypes II and IV, (18) serotypes II and V, (19) serotypes II and VI, (20) serotypes II and VII, (21) serotypes II and VII, (22) serotypes III and IV, (23) serotypes III and V, (24) serotypes III and VI, (25) serotypes III and VII, (26) serotypes III and VIII, (27) serotypes IV and V, (28) serotypes IV and VI, (29) serotypes IV and VII, (30) serotypes IV and VIII, (31) serotypes V and VI, (32) serotypes V and VII, (33) serotypes V and VIII, (34) serotypes VI and VII, (35) serotypes VI and VIII, and (36) serotypes VII and VIII.

Still more preferably, the combinations protect against the following groups of serotypes: (1) serotypes Ia and II, (2) serotypes Ia and V, (3) serotypes Ib and II, (4) serotypes Ib and V, (5) serotypes III and II, and (6) serotypes III and V. Most preferably, the combinations protect against serotypes III and V.

Protection against serotypes II and V is preferably provided by polypeptide antigens. Protection against serotypes Ia, Ib and/or III may be polypeptide or saccharide antigens.

Preferably, the immunogenic composition comprises one or more serogroup V antigens or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358,

GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691. Preferably, the composition comprises a composition of at least two of these GBS antigens or a fragment thereof.

In one embodiment, the immunogenic composition comprises a GBS saccharide antigen and at least two GBS polypeptide antigens or fragments thereof, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or a fragment thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

Preferably, the combination comprises GBS 80 or a fragment thereof. In one embodiment, the GBS polypeptide antigens comprise a combination of two GBS antigens or fragments thereof selected from the antigen group consisting of (1) GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313, (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 656, (16) GBS 80 and GBS 690, and (17) GBS 80 and GBS 691.

Still more preferably, the combination is selected from the antigen group consisting of (1) GBS 80 and GBS 338; (2) GBS 80 and GBS 361, (3) GBS 80 and GBS 305, (4) GBS 80 and GBS 328, (5) GBS 80 and GBS 690, (6) GBS 80 and GBS 691 and (7) GBS 80 and GBS 147. Even more preferably, the combination comprises GBS 80 and GBS 691.

In one embodiment, the composition comprises a combination at least three GBS polypeptide antigens. Preferably, this combination comprises GBS 80 and GBS 691.

Preferably, the immunogenic composition further comprises a GBS polypeptide or a fragment thereof of serogroup II.

The polypeptide antigen

The polypeptide is preferably: (a) a polypeptide comprising an amino acid sequence selected from the group consisting of the even-numbered SEQ IDs 2-10966 from Ref. 3; (b) a polypeptide comprising an amino acid sequence having sequence identity to an amino acid sequence from in (a); or (c) a polypeptide comprising a fragment of an amino acid sequence from (a).

Within (a), preferred SEQ IDs are those which encode GBS1 to GBS689 (see Table IV of reference 3).

Within (b), the degree of sequence identity may vary depending on the amino acid sequence (a) in question, but is preferably greater than 50% (*e.g.* 60%, 70%, 80%, 90%, 95%, 99% or more). Polypeptides within (b) include homologs, orthologs, allelic variants and functional mutants of (a). Typically, 50% identity or more between two proteins is considered to be an indication of functional

equivalence. Identity between proteins is preferably determined by the Smith-Waterman homology search algorithm as implemented in the MPSRCH program (Oxford Molecular), using an affine gap search with parameters *gap open penalty=12* and *gap extension penalty=1*.

Within (c), the length of the fragment may vary depending on the amino acid sequence (a) in question, but the fragment is preferably at least 7 consecutive amino acids from the sequences of (a) *e.g.* 8, 10, 12, 14, 16, 18, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more. Preferably the fragment comprises one or more epitopes from the sequence. Other preferred fragments are the N-terminal signal peptides of SEQ IDs 1-10966 from Ref. 3, SEQ IDs 1-10966 from Ref. 3 without their N-terminal signal peptides, and SEQ IDs 1-10966 from Ref. 3 wherein up to 10 amino acid residues (*i.e.* 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 residues) are deleted from the N-terminus and/or the C-terminus *e.g.* the N-terminal amino acid residue may be deleted.

The polypeptides can, of course, be prepared by various means (*e.g.* recombinant expression, purification from GBS, chemical synthesis *etc.*) and in various forms (*e.g.* native, fusions, glycosylated, non-glycosylated *etc.*). They are preferably prepared in substantially pure form (*i.e.* substantially free from other streptococcal or host cell proteins) or substantially isolated form.

Preferred polypeptide antigens are: GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691, including polypeptides having amino acid sequences with sequence identity thereto *etc.*

The nucleotide and amino acid sequences of GBS80 in Ref. 3 are SEQ ID 8779 and SEQ ID 8780. These sequences are set forth below as SEQ ID NOS 1 and 2:

SEQ ID NO. 1

```
ATGAAATTATCGAAGAAGTTATTGTTTTCGGCTGCTGTTTTAACAATGGTGGCGGGGTCAACTGTTGAACCAGTAGCTCAGTTTGC
GACTGGAATGAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAACAGTAAATATCTATAAATTACAAGCTG
ATAGTTATAAATCGGAAATTACTTCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGCTAAACTTGGTGAC
AATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTTATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAAATTGACAAC
AGTTGAAGCAGCAGATGCAAAAGTTGGAACGATTCTTGAAGAAGGTGTCAGTCTACCTCAAAAAACTAATGCTCAAGGTTTGGTCG
TCGATGCTCTGGATTCAAAAAGTAATGTGAGATACTTGTATGTAGAAGATTTAAAGAATTCACCTTCAAACATTACCAAAGCTTAT
GCTGTACCGTTTGTGTTGGAATTACCAGTTGCTAACTCTACAGGTACAGGTTTCCTTTCTGAAATTAATATTTACCCTAAAAACGT
TGTAACTGATGAACCAAAAACAGATAAAGATGTTAAAAAATTAGGTCAGGACGATGCAGGTTATACGATTGGTGAAGAATTCAAAT
GGTTCTTGAAATCTACAATCCCTGCCAATTTAGGTGACTATGAAAAATTTGAAATTACTGATAAATTTGCAGATGGCTTGACTTAT
AAATCTGTTGGAAAAATCAAGATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACCAACAGTTGATAACCA
AAATACATTAAAAATTACGTTTAAACCAGAGAAATTTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAAG
ATGCTCTTGATAAAGCTACTGCAAATACAGATGATGCGGCATTTTTGGAAATTCCAGTTGCATCAACTATTAATGAAAAAGCAGTT
TTAGGAAAAGCAATTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGACAATCCAAAACCATCTAATCCTCC
AAGAAAACCAGAAGTTCATACTGGTGGAAACGATTTGTAAAGAAAGACTCAACAGAAACACAAACACTAGGTGGTGCTGAGTTTG
ATTTGTTGGCTTCTGATGGGACAGCAGTAAAATGGACAGATGCTCTTATTAAAGCGAATACTAATAAAAACTATATTGCTGGAGAA
GCTGTTACTGGGCAACCAATCAAATTGAAATCACATACAGACGGTACGTTTGAGATTAAAGGTTTGGCTTATGCAGTTGATGCGAA
TGCAGAGGGTACAGCAGTAACTTACAAATTAAAAGAAACAAAAGCACCAGAAGGTTATGTAATCCCTGATAAAGAAATCGAGTTTA
CAGTATCACAAACATCTTATAATACAAAACCAACTGACATCACGGTTGATAGTGCTGATGCAACACCTGATACAATTAAAAACAAC
AAACGTCCTTCAATCCCTAATACTGGTGGTATTGGTACGGCTATCTTTGTCGCTATCGGTGCTGCGGTGATGGCTTTTGCTGTTAA
GGGGATGAAGCGTCGTACAAAAGATAAC
```

SEQ ID NO: 2

```
MKLSKKLLFSAAVLTMVAGSTVEPVAQFATGMSIVRAAEVSQERPAKTTVNIYKLQADSYKSEITSNGGIENKDGEVISNYAKLGD
NVKGLQGVQFKRYKVKTDISVDELKKLTTVEAADAKVGTILEEGVSLPQKTNAQGLVVDALDSKSNVRYLYVEDLKNSPSNITKAY
AVPFVLELPVANSTGTGFLSEINIYPKNVVTDEPKTDKDVKKLGQDDAGYTIGEEFKWFLKSTIPANLGDYEKFEITDKFADGLTY
KSVGKIKIGSKTLNRDEHYTIDEPTVDNQNTLKITFKPEKFKEIAELLKGMTLVKNQDALDKATANTDDAAFLEIPVASTINEKAV
```

LGKAIENTFELQYDHTPDKADNPKPSNPPRKPEVHTGGKRFVKKDSTETQTLGGAEFDLLASDGTAVKWTDALIKANTNKNYIAGE
AVTGQPIKLKSHTDGTFEIKGLAYAVDANAEGTAVTYKLKETKAPEGYVIPDKEIEFTVSQTSYNTKPTDITVDSADATPDTIKNN
KRPSIPNTGGIGTAIFVAIGAAVMAFAVKGMKRRTKDN

The nucleotide and amino acid sequences of GBS 91 in Ref. 3 are SEQ ID 8937 and SEQ ID 8938. These sequences are set forth below as SEQ ID NOS 3 and 4:

SEQ ID NO. 3

ATGAAAAAAGGACAAGTAAATGATACTAAGCAATCTTACTCTCTACGTAAATATAAATTTGGTTTAGCATCAGTAATTTTAGGGTC
ATTCATAATGGTCACAAGTCCTGTTTTTGCGGATCAAACTACATCGGTTCAAGTTAATAATCAGACAGGCACTAGTGTGGATGCTA
ATAATTCTTCCAATGAGACAAGTGCGTCAAGTGTGATTACTTCCAATAATGATAGTGTTCAAGCGTCTGATAAAGTTGTAAATAGT
CAAAATACGGCAACAAAGGACATTACTACTCCTTTAGTAGAGACAAAGCCAATGGTGGAAAAAACATTACCTGAACAAGGGAATTA
TGTTTATAGCAAAGAAACCGAGGTGAAAAATACACCTTCAAAATCAGCCCCAGTAGCTTTCTATGCAAAGAAAGGTGATAAAGTTT
TCTATGACCAAGTATTTAATAAAGATAATGTGAAATGGATTTCATATAAGTCTTTTTGTGGCGTACGTCGATACGCAGCTATTGAG
TCACTAGATCCATCAGGAGGTTCAGAGACTAAAGCACCTACTCCTGTAACAAATTCAGGAAGCAATAATCAAGAGAAAATAGCAAC
GCAAGGAAATTATACATTTTCACATAAAGTAGAAGTAAAAAATGAAGCTAAGGTAGCGAGTCCAACTCAATTTACATTGGACAAAG
GAGACAGAATTTTTTACGACCAAATACTAACTATTGAAGGAAATCAGTGGTTATCTTATAAATCATTCAATGGTGTTCGTCGTTTT
GTTTTGCTAGGTAAAGCATCTTCAGTAGAAAAAACTGAAGATAAAGAAAAAGTGTCTCCTCAACCACAAGCCCGTATTACTAAAAC
TGGTAGACTGACTATTTCTAACGAAACAACTACAGGTTTTGATATTTTAATTACGAATATTAAAGATGATAACGGTATCGCTGCTG
TTAAGGTACCGGTTTGGACTGAACAAGGAGGGCAAGATGATATTAAATGGTATACAGCTGTAACTACTGGGGATGGCAACTACAAA
GTAGCTGTATCATTTGCTGACCATAAGAATGAGAAGGGTCTTTATAATATTCATTTATACTACCAAGAAGCTAGTGGGACACTTGT
AGGTGTAACAGGAACTAAAGTGACAGTAGCTGGAACTAATTCTTCTCAAGAACCTATTGAAAATGGTTTAGCAAAGACTGGTGTTT
ATAATATTATCGGAAGTACTGAAGTAAAAAATGAAGCTAAAATATCAAGTCAGACCCAATTTACTTTAGAAAAAGGTGACAAAATA
AATTATGATCAAGTATTGACAGCAGATGGTTACCAGTGGATTTCTTACAAATCTTATAGTGGTGTTCGTCGCTATATTCCTGTGAA
AAAGCTAACTACAAGTAGTGAAAAAGCGAAAGATGAGGCGACTAAACCGACTAGTTATCCCAACTTACCTAAAACAGGTACCTATA
CATTTACTAAAACTGTAGATGTGAAAAGTCAACCTAAAGTATCAAGTCCAGTGGAATTTAATTTTCAAAAGGGTGAAAAAATACAT
TATGATCAAGTGTTAGTAGTAGATGGTCATCAGTGGATTTCATACAAGAGTTATTCCGGTATTCGTCGCTATATTGAAATT

SEQ ID NO. 4

MKKGQVNDTKQSYSLRKYKFGLASVILGSFIMVTSPVFADQTTSVQVNNQTGTSVDANNSSNETSASSVITSNNDSVQASDKVVNS
QNTATKDITTPLVETKPMVEKTLPEQGNYVYSKETEVKNTPSKSAPVAFYAKKGDKVFYDQVFNKDNVKWISYKSFCGVRRYAAIE
SLDPSGGSETKAPTPVTNSGSNNQEKIATQGNYTFSHKVEVKNEAKVASPTQFTLDKGDRIFYDQILTIEGNQWLSYKSFNGVRRF
VLLGKASSVEKTEDKEKVSPQPQARITKTGRLTISNETTTGFDILITNIKDDNGIAAVKVPVWTEQGGQDDIKWYTAVTTGDGNYK
VAVSFADHKNEKGLYNIHLYYQEASGTLVGVTGTKVTVAGTNSSQEPIENGLAKTGVYNIIGSTEVKNEAKISSQTQFTLEKGDKI
NYDQVLTADGYQWISYKSYSGVRRYIPVKKLTTSSEKAKDEATKPTSYPNLPKTGTYTFTKTVDVKSQPKVSSPVEFNFQKGEKIH
YDQVLVVDGHQWISYKSYSGIRRYIEI

The nucleotide and amino acid sequences of GBS 104 in Ref. 3 are SEQ ID 8777 and SEQ ID 8778. These sequences are set forth below as SEQ ID NOS 5 and 6:

SEQ ID NO. 5

ATGAAAAAGAGACAAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCCAAATTCCATTTGGTATATTGGTACAAGG
TGAAACCCAAGATACCAATCAAGCACTTGGAAAAGTAATTGTTAAAAAAACGGGAGACAATGCTACACCATTAGGCAAAGCGACTT
TTGTGTTAAAAAATGACAATGATAAGTCAGAAACAAGTCACGAAACGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAACATAAAA
CCTGGAGACTACACATTAAGAGAAGAAACAGCACCAATTGGTTATAAAAAAACTGATAAAACCTGGAAAGTTAAAGTTGCAGATAA
CGGAGCAACAATAATCGAGGGTATGGATGCAGATAAAGCAGAGAAACGAAAAGAAGTTTTGAATGCCCAATATCCAAAATCAGCTA
TTTATGAGGATACAAAAGAAAATTACCCATTAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAATCCAATA
AATGGAAAAGATGGTCGAAGAGAGATTGCTGAAGGTTGGTTATCAAAAAAAATTACAGGGGTCAATGATCTCGATAAGAATAAATA
TAAAATTGAATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAACCACTAGATGTCGTTGTGCTATTAGATA
ATTCAAATAGTATGAATAATGAAAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAAAGCTGATTGATAAA
ATTACATCAAATAAAGACAATAGAGTAGCTCTTGTGACATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG
AGTTGCCGATCAAAATGGTAAAGCGCTGAATGATAGTGTATCATGGGATTATCATAAAACTACTTTTACAGCAACTACACATAATT
ACAGTTATTTAAATTTAACAAATGATGCTAACGAAGTTAATATTCTAAAGTCAAGAATTCCAAAGGAAGCGGAGCATATAAATGGG
GATCGCACGCTCTATCAATTTGGTGCGACATTTACTCAAAAAGCTCTAATGAAAGCAAATGAAATTTTAGAGACACAAAGTTCTAA
TGCTAGAAAAAAACTTATTTTTCACGTAACTGATGGTGTCCCTACGATGTCTTATGCCATAAATTTTAATCCTTATATATCAACAT
CTTACCAAAACCAGTTTAATTCTTTTTTAAATAAAATACCAGATAGAAGTGGTATTCTCCAAGAGGATTTTATAATCAATGGTGAT
GATTATCAAATAGTAAAAGGAGATGGAGAGAGTTTTAAACTGTTTTCGGATAGAAAAGTTCCTGTTACTGGAGGAACGACACAAGC
AGCTTATCGAGTACCGCAAAATCAACTCTCTGTAATGAGTAATGAGGGATATGCAATTAATAGTGGATATATTTATCTCTATTGGA
GAGATTACAACTGGGTCTATCCATTTGATCCTAAGACAAAGAAAGTTTCTGCAACGAAACAAATCAAAACTCATGGTGAGCCAACA
ACATTATACTTTAATGGAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGGATTGGTGTAAACGGAGATCCTGGTGCAAC
TCCTCTTGAAGCTGAGAAATTTATGCAATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAATAAAATTTATG
ATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAAACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATG
ATTGAATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTGGTTGGAAATGATGGCAGTCAATTAAAAAATGG
TGTGGCTCTTGGTGGACCAAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGACATCTCAAACCATCAAAA

TCAATCATTTGAACTTAGGAAGTGGACAAAAAGTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAAATTT
TACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAGAACCAAATACTATTCGTGATTTCCCAATTCCCAAAATTCG
TGATGTTCGTGAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGGTTGAATTTATTAAAGTTAATAAAGACAAAC
ATTCAGAATCGCTTTTGGGAGCTAAGTTTCAACTTCAGATAGAAAAAGATTTTTCTGGGTATAAGCAATTTGTTCCAGAGGGAAGT
GATGTTACAACAAAGAATGATGGTAAAATTTATTTTAAAGCACTTCAAGATGGTAACTATAAATTATATGAAATTTCAAGTCCAGA
TGGCTATATAGAGGTTAAAACGAAACCTGTTGTGACATTTACAATTCAAAATGGAGAAGTTACGAACCTGAAAGCAGATCCAAATG
CTAATAAAAATCAAATCGGGTATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCCAAACGCCCACCAGGTGTTTTTCCT
AAAACAGGGGGAATTGGTACAATTGTCTATATATTAGTTGGTTCTACTTTTATGATACTTACCATTTGTTCTTTCCGTCGTAAACA
ATTG

SEQ ID NO. 6

MKKRQKIWRGLSVTLLILSQIPFGILVQGETQDTNQALGKVIVKKTGDNATPLGKATFVLKNDNDKSETSHETVEGSGEATFENIK
PGDYTLREETAPIGYKKTDKTWKVKVADNGATIIEGMDADKAEKRKEVLNAQYPKSAIYEDTKENYPLVNVEGSKVGEQYKALNPI
NGKDGRREIAEGWLSKKITGVNDLDKNKYKIELTVEGKTTVETKELNQPLDVVVLLDNSNSMNNERANNSQRALKAGEAVEKLIDK
ITSNKDNRVALVTYASTIFDGTEATVSKGVADQNGKALNDSVSWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHING
DRTLYQFGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTMSYAINFNPYISTSYQNQFNSFLNKIPDRSGILQEDFIINGD
DYQIVKGDGESFKLFSDRKVPVTGGTTQAAYRVPQNQLSVMSNEGYAINSGYIYLYWRDYNWVYPFDPKTKKVSATKQIKTHGEPT
TLYFNGNIRPKGYDIFTVGIGVNGDPGATPLEAEKFMQSISSKTENYTNVDDTNKIYDELNKYFKTIVEEKHSIVDGNVTDPMGEM
IEFQLKNGQSFTHDDYVLVGNDGSQLKNGVALGGPNSDGGILKDVTVTYDKTSQTIKINHLNLGSGQKVVLTYDVRLKDNYISNKF
YNTNNRTTLSPKSEKEPNTIRDFPIPKIRDVREFPVLTISNQKKMGEVEFIKVNKDKHSESLLGAKFQLQIEKDFSGYKQFVPEGS
DVTTKNDGKIYFKALQDGNYKLYEISSPDGYIEVKTKPVVTFTIQNGEVTNLKADPNANKNQIGYLEGNGKHLITNTPKRPPGVFP
KTGGIGTIVYILVGSTFMILTICSFRRKQL

The nucleotide and amino acid sequences of GBS 147 in Ref. 3 are SEQ ID 8525 and SEQ ID 8526. These sequences are set forth below as SEQ ID NOS 7 and 8:

SEQ ID NO. 7

GTGGATAAACATCACTCAAAAAAGGCTATTTTAAAGTTAACACTTATAACAACTAGTATTTTATTAATGCATAGCAATCAAGTGAATGCAGAGGAG
CAAGAATTAAAAAACCAAGAGCAATCACCTGTAATTGCTAATGTTGCTCAACAGCCATCGCCATCGGTAACTACTAATACTGTTGAAAAAACATCT
GTAACAGCTGCTTCTGCTAGTAATACAGCGAAAGAAATGGGTGATACATCTGTAAAAAATGACAAAACAGAAGATGAATTATTAGAAGAGTTATCT
AAAAACCTTGATACGTCTAATTTGGGGGCTGATCTTGAAGAAGAATATCCCTCTAAACCAGAGACAACCAACAATAAAGAAAGCAATGTAGTAACA
AATGCTTCAACTGCAATAGCACAGAAAGTTCCCTCAGCATATGAAGAGGTGAAGCCAGAAAGCAAGTCATCGCTTGCTGTTCTTGATACATCTAAA
ATAACAAAATTACAAGCCATAACCCAAAGAGGAAAGGGAAATGTAGTAGCTATTATTGATACTGGCTTTGATATTAACCATGATATTTTTCGTTTA
GATAGCCCAAAAGATGATAAGCACAGCTTTAAAACTAAGACAGAATTTGAGGAATTAAAAGCAAAACATAATATCACTTATGGGAAATGGGTTAAC
GATAAGATTGTTTTTGCACATAACTACGCCAACAATACAGAAACGGTGGCTGATATTGCAGCAGCTATGAAAGATGGTTATGGTTCAGAAGCAAAG
AATATTTCGCATGGTACACACGTTGCTGGTATTTTTGTAGGTAATAGTAAACGTCCAGCAATCAATGGTCTTCTTTTAGAAGGTGCAGCGCCAAAT
GCTCAAGTCTTATTAATGCGTATTCCAGATAAAATTGATTCGGACAAATTTGGTGAAGCATATGCTAAAGCAATCACAGACGCTGTTAATCTAGGA
GCAAAAACGATTAATATGAGTATTGGAAAAACAGCTGATTCTTTAATTGCTCTCAATGATAAAGTTAAATTAGCACTTAAATTAGCTTCTGAGAAG
GGCGTTGCAGTTGTTGTGGCTGCCGGAAATGAAGGCGCATTTGGTATGGATTATAGCAAACCATTATCAACTAATCCTGACTACGGTACGGTTAAT
AGTCCAGCTATTTCTGAAGATACTTTGAGTGTTGCTAGCTATGAATCACTTAAAACTATCAGTGAGGTCGTTGAAACAACTATTGAAGGTAAGTTA
GTTAAGTTGCCGATTGTGACTTCTAAACCTTTTGACAAAGGTAAGGCCTACGATGTGGTTTATGCCAATTATGGTGCAAAAAAAGACTTTGAAGGT
AAGGACTTTAAAGGTAAGATTGCATTAATTGAGCGTGGTGGTGGACTTGATTTTATGACTAAAATCACTCATGCTACAAATGCAGGTGTTGTTGGT
ATCGTTATTTTTAACGATCAAGAAAAACGTGGAAATTTTCTAATTCCTTACCGTGAATTACCTGTGGGGATTATTAGTAAAGTAGATGGCGAGCGT
ATAAAAAATACTTCAAGTCAGTTAACATTTAACCAGAGTTTTGAAGTAGTTGATAGCCAAGGTGGTAATCGTATGCTGGAACAATCAAGTTGGGGC
GTGACAGCTGAAGGAGCAATCAAGCCTGATGTAACAGCTTCTGGCTTTGAAATTTATTCTTCAACCTATAATAATCAATACCAAACAATGTCTGGT
ACAAGTATGGCTTCACCACATGTTGCAGGATTAATGACAATGCTTCAAAGTCATTTGGCTGAGAAATATAAAGGGATGAATTTAGATTCTAAAAAA
TTGCTAGAATTGTCTAAAAACATCCTCATGAGCTCAGCAACAGCATTATATAGTGAAGAGGATAAGGCGTTTTATTCACCACGTCAGCAAGGTGCA
GGTGTAGTTGATGCTGAAAAAGCTATCCAAGCTCAATATTATATTACTGGAAACGATGGCAAAGCTAAAATTAATCTCAAACGAATGGGAGATAAA
TTTGATATCACAGTTACAATTCATAAACTTGTAGAAGGTGTCAAAGAATTGTATTATCAAGCTAATGTAGCAACAGAACAAGTAAATAAAGGTAAA
TTTGCCCTTAAACCACAAGCCTTGCTAGATACTAATTGGCAGAAAGTAATTCTTCGTGATAAAGAAACACAAGTTCGATTTACTATTGATGCTAGT
CAATTTAGTCAGAAATTAAAAGAACAGATGGCAAATGGTTATTTCTTAGAAGGTTTTGTACGTTTTAAAGAAGCCAAGGATAGTAATCAGGAGTTA
ATGAGTATTCCTTTTGTAGGATTTAATGGTGATTTTGCGAACTTACAAGCACTTGAAACACCGATTTATAAGACGCTTTCTAAAGGTAGTTTCTAC
TATAAACCAAATGATACAACTCATAAAGACCAATTGGAGTACAATGAATCAGCTCCTTTTGAAAGCAACAACTATACTGCCTTGTTAACACAATCA
GCGTCTTGGGGCTATGTTGATTATGTCAAAAATGGTGGGGAGTTAGAATTAGCACCGGAGAGTCCAAAAAGAATTATTTTAGGAACTTTTGAGAAT
AAGGTTGAGGATAAAACAATTCATCTTTTGGAAAGAGATGCAGCGAATAATCCATATTTTGCCATTTCTCCAAATAAAGATGGAAATAGGGACGAA
ATCACTCCCCAGGCAACTTTCTTAAGAAATGTTAAGGATATTTCTGCTCAAGTTCTAGATCAAAATGGAAATGTTATTTGGCAAAGTAAGGTTTTA
CCATCTTATCGTAAAAATTTCCATAATAATCCAAAGCAAAGTGATGGTCATTATCGTATGGATGCTCTTCAGTGGAGTGGTTTAGATAAGGATGGC
AAAGTTGTAGCAGATGGTTTTTATACTTATCGCTTACGTTACACACCAGTAGCAGAAGGAGCAAATAGTCAGGAGTCAGACTTTAAAGTACAAGTA
AGTACTAAGTCACCAAATCTTCCTTCACGAGCTCAGTTTGATGAAACTAATCGAACATTAAGCTTAGCCATGCCTAAGGAAAGTAGTTATGTTCCT
ACATATCGTTTACAATTAGTTTTATCTCATGTTGTAAAAGATGAAGAATATGGGGATGAGACTTCTTACCATTATTTCCATATAGATCAAGAAGGT
AAAGTGACACTTCCTAAAACGGTTAAGATAGGAGAGAGTGAGGTTGCGGTAGACCCTAAGGCCTTGACACTTGTTGTGGAAGATAAAGCTGGTAAT
TTCGCAACGGTAAAATTGTCTGATCTCTTGAATAAGGCAGTAGTATCAGAGAAAGAAAACGCTATAGTAATTTCTAACAGTTTCAAATATTTTGAT
AACTTGAAAAAAGAACCTATGTTTATTTCTAAAAAAGAAAAAGTAGTAAACAAGAATCTAGAAGAAATAATATTAGTTAAGCCGCAAACTACAGTT
ACTACTCAATCATTGTCTAAAGAAATAACTAAATCAGGAAATGAGAAAGTCCTCACTTCTACAAACAATAATAGTAGCAGAGTAGCTAAGATCATA
TCACCTAAACATAACGGGGATTCTGTTAACCATACCTTACCTAGTACATCAGATAGAGCAACGAATGGTCTATTTGTTGGTACTTTGGCATTGTTA
TCTAGTTTACTTCTTTATTTGAAACCCAAAAAGACTAAAAATAATAGTAAA

SEQ ID NO. 8

VDKHHSKKAILKLTLITTSILLMHSNQVNAEEQELKNQEQSPVIANVAQQPSPSVTTNTVEKTSVTAASASNTAKEMGDTSVKNDKTEDELLEELS
KNLDTSNLGADLEEEYPSKPETTNNKESNVVTNASTAIAQKVPSAYEEVKPESKSSLAVLDTSKITKLQAITQRGKGNVVAIIDTGFDINHDIFRL

DSPKDDKHSFKTKTEFEELKAKHNITYGKWVNDKIVFAHNYANNTETVADIAAAMKDGYGSEAKNISHGTHVAGIFVGNSKRPAINGLLLEGAAPN
AQVLLMRIPDKIDSDKFGEAYAKAITDAVNLGAKTINMSIGKTADSLIALNDKVKLALKLASEKGVAVVVAAGNEGAFGMDYSKPLSTNPDYGTVN
SPAISEDTLSVASYESLKTISEVVETTIEGKLVKLPIVTSKPFDKGKAYDVVYANYGAKKDFEGKDFKGKIALIERGGGLDFMTKITHATNAGVVG
IVIFNDQEKRGNFLIPYRELPVGIISKVDGERIKNTSSQLTFNQSFEVVDSQGGNRMLEQSSWGVTAEGAIKPDVTASGFEIYSSTYNNQYQTMSG
TSMASPHVAGLMTMLQSHLAEKYKGMNLDSKKLLELSKNILMSSATALYSEEDKAFYSPRQQGAGVVDAEKAIQAQYYITGNDGKAKINLKRMGDK
FDITVTIHKLVEGVKELYYQANVATEQVNKGKFALKPQALLDTNWQKVILRDKETQVRFTIDASQFSQKLKEQMANGYFLEGFVRFKEAKDSNQEL
MSIPFVGFNGDFANLQALETPIYKTLSKGSFYYKPNDTTHKDQLEYNESAPFESNNYTALLTQSASWGYVDYVKNGGELELAPESPKRIILGTFEN
KVEDKTIHLLERDAANNPYFAISPNKDGNRDEITPQATFLRNVKDISAQVLDQNGNVIWQSKVLPSYRKNFHNNPKQSDGHYRMDALQWSGLDKDG
KVVADGFYTYRLRYTPVAEGANSQESDFKVQVSTKSPNLPSRAQFDETNRTLSLAMPKESSYVPTYRLQLVLSHVVKDEEYGDETSYHYFHIDQEG
KVTLPKTVKIGESEVAVDPKALTLVVEDKAGNFATVKLSDLLNKAVVSEKENAIVISNSFKYFDNLKKEPMFISKKEKVVNKNLEEIILVKPQTTV
TTQSLSKEITKSGNEKVLTSTNNNSSRVAKIISPKHNGDSVNHTLPSTSDRATNGLFVGTLALLSSLLLYLKPKKTKNNSK

The nucleotide and amino acid sequences of GBS 173 in Ref. 3 are SEQ ID 8787 and SEQ ID 8788. These sequences are set forth below as SEQ ID NOS 9 and 10:

SEQ ID NO. 9

ATGAAACGTAAATACTTTATTCTTAATACGGTGACGGTTTTAACGTTAGCTGCTGCAATGAATACTAGCAGTATCTATGCTAATAGTACTGAGACA
AGTGCTTCAGTAGTTCCTACTACAAATACTATCGTTCAAACTAATGACAGTAATCCTACCGCAAAATTTGTATCAGAATCAGGACAATCTGTAATA
GGTCAAGTAAAACCAGATAATTCTGCGGCGCTTACAACAGTTGACACGCCTCATCATATTTCAGCTCCAGATGCTTTAAAAACAACTCAATCAAGT
CCTGTCGTTGAGAGTACTTCTACTAAGTTAACTGAAGAGACTTACAAACAAAAAGATGGTCAAGATTTAGCCAACATGGTGAGAAGTGGTCAAGTT
ACTAGTGAGGAACTCGTTAATATGGCATACGATATTATTGCTAAAGAAAACCCATCTTTAAATGCAGTCATTACTACTAGACGCCAAGAAGCTATT
GAAGAGGCTAGAAAACTTAAAGATACCAATCAGCCGTTTTTAGGTGTTCCCTTGTTAGTCAAGGGGTTAGGGCACAGTATTAAAGGTGGTGAAACC
AATAATGGCTTGATCTATGCAGATGGAAAAATTAGCACATTTGACAGTAGCTATGTCAAAAAATATAAAGATTTAGGATTTATTATTTTAGGACAA
ACGAACTTTCCAGAGTATGGGTGGCGTAATATAACAGATTCTAAATTATACGGTCTAACGCATAATCCTTGGGATCTTGCTCATAATGCTGGTGGC
TCTTCTGGTGGAAGTGCAGCAGCCATTGCTAGCGGAATGACGCCAATTGCTAGCGGTAGTGATGCTGGTGGTTCTATCCGTATTCCATCTTCTTGG
ACGGGCTTGGTAGGTTTAAAACCAACAAGAGGATTGGTGAGTAATGAAAAGCCAGATTCGTATAGTACAGCAGTTCATTTTCCATTAACTAAGTCA
TCTAGAGACGCAGAAACATTATTAACTTATCTAAAGAAAAGCGATCAAACGCTAGTATCAGTTAATGATTTAAAATCTTTACCAATTGCTTATACT
TTGAAATCACCAATGGGAACAGAAGTTAGTCAAGATGCTAAAAACGCTATTATGGACAACGTCACATTCTTAAGAAAACAAGGATTCAAAGTAACA
GAGATAGACTTACCAATTGATGGTAGAGCATTAATGCGTGATTATTCAACCTTGGCTATTGGCATGGGAGGAGCTTTTTCAACAATTGAAAAAGAC
TTAAAAAAACATGGTTTTACTAAAGAAGACGTTGATCCTATTACTTGGGCAGTTCATGTTATTTATCAAAATTCAGATAAGGCTGAACTTAAGAAA
TCTATTATGGAAGCCCAAAAACATATGGATGATTATCGTAAGGCAATGGAGAAGCTTCACAAGCAATTTCCTATTTTCTTATCGCCAACGACCGCA
AGTTTAGCCCCTCTAAATACAGATCCATATGTAACAGAGGAAGATAAAAGAGCGATTTATAATATGGAAAACTTGAGCCAAGAAGAAAGAATTGCT
CTCTTTAATCGCCAGTGGGAGCCTATGTTGCGTAGAACACCTTTTACACAAATTGCTAATATGACAGGACTCCCAGCTATCAGTATCCCGACTTAC
TTATCTGAGTCTGGTTTACCCATAGGGACGATGTTAATGGCAGGTGCAAACTATGATATGGTATTAATTAAATTTGCAACTTTCTTTGAAAAACAT
CATGGTTTTAATGTTAAATGGCAAAGAATAATAGATAAAGAAGTGAAACCATCTACTGGCCTAATACAGCCTACTAACTCCCTCTTTAAAGCTCAT
TCATCATTAGTAAATTTAGAAGAAAATTCACAAGTTACTCAAGTATCTATCTCTAAAAAATGGATGAAATCGTCTGTTAAAAATAAACCATCCGTA
ATGGCATATCAAAAAGCACTTCCTAAAACAGGTGATACAGAATCAAGCCTATCTCCAGTTTTAGTAGTAACCCTTTTATTAGCTTGTTTTAGCTTT
GTAACAAAAAAGAATCAGAAAAGT

SEQ ID NO. 10

MKRKYFILNTVTVLTLAAAMNTSSIYANSTETSASVVPTTNTIVQTNDSNPTAKFVSESGQSVIGQVKPDNSAALTTVDTPHHISAPDALKTTQSS
PVVESTSTKLTEETYKQKDGQDLANMVRSGQVTSEELVNMAYDIIAKENPSLNAVITTRRQEAIEEARKLKDTNQPFLGVPLLVKGLGHSIKGGET
NNGLIYADGKISTFDSSYVKKYKDLGFIILGQTNFPEYGWRNITDSKLYGLTHNPWDLAHNAGGSSGGSAAAIASGMTPIASGSDAGGSIRIPSSW
TGLVGLKPTRGLVSNEKPDSYSTAVHFPLTKSSRDAETLLTYLKKSDQTLVSVNDLKSLPIAYTLKSPMGTEVSQDAKNAIMDNVTFLRKQGFKVT
EIDLPIDGRALMRDYSTLAIGMGGAFSTIEKDLKKHGFTKEDVDPITWAVHVIYQNSDKAELKKSIMEAQKHMDDYRKAMEKLHKQFPIFLSPTTA
SLAPLNTDPYVTEEDKRAIYNMENLSQEERIALFNRQWEPMLRRTPFTQIANMTGLPAISIPTYLSESGLPIGTMLMAGANYDMVLIKFATFFEKH
HGFNVKWQRIIDKEVKPSTGLIQPTNSLFKAHSSLVNLEENSQVTQVSISKKWMKSSVKNKPSVMAYQKALPKTGDTESSLSPVLVVTLLLACFSF
VTKKNQKS

The nucleotide and amino acid sequences of GBS 276 in Ref. 3 are SEQ ID 8941 and SEQ ID 8942. These sequences are set forth below as SEQ ID NOS 11 and 12:

SEQ ID NO. 11

TTGCGTAAAAAACAAAAACTACCATTTGATAAACTTGCCATTGCGCTTATATCTACGAGCATCTTGCTCAATGCACAATCAGACATTAAAGCAAAT
ACTGTGACAGAAGACACTCCTGCTACCGAACAAGCCGTAGAACCCCCACAACCAATAGCAGTTTCTGAGGAATCACGATCATCAAAGGAAACTAAA
ACCTCACAAACTCCTAGTGATGTAGGAGAAACAGTAGCAGATGACGCTAATGATCTAGCCCCTCAAGCTCCTGCTAAAACTGCTGATACACCAGCA
ACCTCAAAAGCGACTATTAGGGATTTGAACGACCCTTCTCATGTCAAAACCCTGCAGGAAAAAGCAGGCAAGGGAGCTGGGACCGTTGTTGCAGTG
ATTGATGCTGGTTTTGATAAAAATCATGAAGCGTGGCGCTTAACAGACAAAACTAAAGCACGTTACCAATCAAAAGAAAATCTTGAAAAAGCTAAA
AAAGAGCACGGTATTACCTATGGCGAGTGGGTCAATGATAAGGTTGCTTATTACCACGACTATAGTAAAGATGGTAAAAACGCTGTTGATCAAGAA
CACGGCACACACGTGTCAGGGATCTTGTCAGGAAATGCTCCATCTGAAATGAAAGAACCTTACCGCCTAGAAGGTGCGATGCCTGAGGCTCAATTG
CTTTTGATGCGTGTCGAAATTGTAAATGGACTAGCAGACTATGCTCGTAACTACGCTCAAGCTATCAGAGATGCTGTCAACTTGGGAGCTAAGGTG
ATTAATATGAGCTTTGGTAATGCTGCACTAGCTTACGCCAACCTTCCAGACGAAACCAAAAAAGCCTTTGACTATGCCAAATCAAAAGGTGTTAGC
ATTGTGACCTCAGCTGGTAATGATAGTAGCTTTGGGGGCAAGCCCCGTCTACCTCTAGCAGATCATCCTGATTATGGGGTGGTTGGGACACCTGCA
GCGGCAGATTCAACATTGACAGTTGCTTCTTACAGCCCAGATAAACAGCTCACTGAAACTGCTACGGTCAAAACAGACGATCATCAAGATAAAGAA
ATGCCTGTTATTTCAACAAACCGTTTTGAGCCAAACAAGGCTTACGACTATGCTTATGCTAATCGTGGTACGAAAGAGGATGATTTTAAGGATGTC
GAAGGTAAGATTGCCCTTATTGAACGTGGCGATATTGATTTCAAAGATAAGATTGCAAACGCTAAAAAAGCTGGTGCTGTAGGGGTCTTGATCTAT
GACAATCAAGACAAGGGCTTCCCGATTGAATTGCCAAATGTTGACCAGATGCCTGCGGCCTTTATCAGTCGAAGAGACGGTCTCTTATTAAAAGAC
AATCCCCCAAAAACCATTACCTTCAATGCGACACCTAAGGTATTGCCAACAGCAAGTGGCACCAAACTAAGCCGCTTCTCAAGCTGGGGTCTGACA
GCTGACGGCAATATTAAACCGGATATTGCAGCACCCGGCCAAGATATTTTGTCATCAGTGGCTAACAACAAGTATGCCAAACTTTCTGGAACTAGT
ATGTCTGCACCATTGGTAGCGGGTATCATGGGACTGTTGCAAAAGCAATATGAGACACAGTATCCTGATATGACACCATCAGAGCGTCTTGATTTA
GCTAAGAAAGTATTGATGAGCTCAGCAACTGCCCTATATGATGAAGATGAAAAAGCTTATTTTTCTCCTCGCCAACAGGGAGCAGGAGCAGTCGAT

GCTAAAAAAGCTTCAGCAGCAACGATGTATGTAACAGATAAGGACAATACCTCAAGCAAGGTTCACCTGAACAATGTTTCTGATAAATTTGAAGTA
ACAGTAACAGTTCACAACAAATCTGATAAACCTCAAGAGTTGTATTACCAAGTAACTGTTCAAACAGATAAAGTAGATGGAAAACACTTTGCCTTG
GCTCCTAAAGCATTGTATGAGACATCATGGCAAAAAATCACAATTCCAGCCAATAGCAGCAAACAAGTCACCGTTCCAATCGATGCTAGTCGATTT
AGCAAGGACTTGCTTGCCCAAATGAAAAATGGCTATTTCTTAGAAGGTTTTGTTCGTTTCAAACAAGATCCTACAAAAGAAGAGCTTATGAGCATT
CCATATATTGGTTTCCGAGGTGATTTTGGCAATCTGTCAGCCTTAGAAAAACCAATCTATGATAGCAAAGACGGTAGCAGCTACTATCATGAAGCA
AATAGTGATGCCAAAGACCAATTAGATGGTGATGGATTACAGTTTTACGCTCTGAAAAATAACTTTACAGCACTTACCACAGAGTCTAACCCATGG
ACGATTATTAAAGCTGTCAAAGAAGGGGTTGAAAACATAGAGGATATCGAATCTTCAGAGATCACAGAAACCATTTTTGCAGGTACTTTTGCAAAA
CAAGACGATGATAGCCACTACTATATCCACCGTCACGCTAATGGCAAACCATATGCTGCGATCTCTCCAAATGGGGACGGTAACAGAGATTATGTC
CAATTCCAAGGTACTTTCTTGCGTAATGCTAAAAACCTTGTGGCTGAAGTCTTGGACAAAGAAGGAAATGTTGTTTGGACAAGTGAGGTAACCGAG
CAAGTTGTTAAAAACTACAACAATGACTTGGCAAGCACACTTGGTTCAACCCGTTTTGAAAAAACGCGTTGGGACGGTAAAGATAAAGACGGCAAA
GTTGTTGCTAACGGAACCTACACCTATCGTGTTCGCTACACGCCGATTAGCTCAGGTGCAAAAGAACAACACACTGATTTTGATGTGATTGTAGAC
AATACGACACCTGAAGTCGCAACATCGGCAACATTCTCAACAGAAGATAGTCGTTTGACACTTGCATCTAAACCAAAAACCAGCCAACCGGTTTAC
CGTGAGCGTATTGCTTACACTTATATGGATGAGGATCTGCCAACAACAGAGTATATTTCTCCAAATGAAGATGGTACCTTTACTCTTCCTGAAGAG
GCTGAAACAATGGAAGGCGCTACTGTTCCATTGAAAATGTCAGACTTTACTTATGTTGTTGAAGATATGGCTGGTAACATCACTTATACACCAGTG
ACTAAGCTATTGGAGGGCCACTCTAATAAGCCAGAACAAGACGGTTCAGATCAAGCACCAGACAAGAAACCAGAAGCTAAACCAGAACAAGACGGT
TCAGGTCAAACACCAGATAAAAAAAAAGAAACTAAACCAGAAAAAGATAGTTCAGGTCAAACACCAGGTAAAACTCCTCAAAAAGGTCAATCTTCT
CGTACTCTAGAGAAACGATCTTCTAAGCGTGCTTTAGCTACAAAAGCATCAACAAGAGATCAGTTACCAACGACTAATGACAAGGATACAAATCGT
TTACATCTCCTTAAGTTAGTTATGACCACTTTCTTCTTGGGA

SEQ ID NO. 12

MRKKQKLPFDKLAIALISTSILLNAQSDIKANTVTEDTPATEQAVEPPQPIAVSEESRSSKETKTSQTPSDVGETVADDANDLAPQ
APAKTADTPATSKATIRDLNDPSHVKTLQEKAGKGAGTVVAVIDAGFDKNHEAWRLTDKTKARYQSKENLEKAKKEHGITYGEWVN
DKVAYYHDYSKDGKNAVDQEHGTHVSGILSGNAPSEMKEPYRLEGAMPEAQLLLMRVEIVNGLADYARNYAQAIRDAVNLGAKVIN
MSFGNAALAYANLPDETKKAFDYAKSKGVSIVTSAGNDSSFGGKPRLPLADHPDYGVVGTPAAADSTLTVASYSPDKQLTETATVK
TDDHQDKEMPVISTNRFEPNKAYDYAYANRGTKEDDFKDVEGKIALIERGDIDFKDKIANAKKAGAVGVLIYDNQDKGFPIELPNV
DQMPAAFISRRDGLLLKDNPPKTITFNATPKVLPTASGTKLSRFSSWGLTADGNIKPDIAAPGQDILSSVANNKYAKLSGTSMSAP
LVAGIMGLLQKQYETQYPDMTPSERLDLAKKVLMSSATALYDEDEKAYFSPRQQGAGAVDAKKASAATMYVTDKDNTSSKVHLNNV
SDKFEVTVTVHNKSDKPQELYYQVTVQTDKVDGKHFALAPKALYETSWQKITIPANSSKQVTVPIDASRFSKDLLAQMKNGYFLEG
FVRFKQDPTKEELMSIPYIGFRGDFGNLSALEKPIYDSKDGSSYYHEANSDAKDQLDGDGLQFYALKNNFTALTTESNPWTIIKAV
KEGVENIEDIESSEITETIFAGTFAKQDDDSHYYIHRHANGKPYAAISPNGDGNRDYVQFQGTFLRNAKNLVAEVLDKEGNVVWTS
EVTEQVVKNYNNDLASTLGSTRFEKTRWDGKDKDGKVVANGTYTYRVRYTPISSGAKEQHTDFDVIVDNTTPEVATSATFSTEDSR
LTLASKPKTSQPVYRERIAYTYMDEDLPTTEYISPNEDGTFTLPEEAETMEGATVPLKMSDFTYVVEDMAGNITYTPVTKLLEGHS
NKPEQDGSDQAPDKKPEAKPEQDGSGQTPDKKKETKPEKDSSGQTPGKTPQKGQSSRTLEKRSSKRALATKASTRDQLPTTNDKDT
NRLHLLKLVMTTFFLG

The nucleotide and amino acid sequences of GBS 305 in Ref. 3 are SEQ ID 207 and SEQ ID 208. These sequences are set forth below as SEQ ID NOS 13 and 14:

SEQ ID NO. 13

ATGGGACGAGTAATGAAAACAATAACAACATTTGAAAATAAAAAAGTTTTAGTCCTTGGTTTAGCACGATCTGGAGAAGCTGCTGC
ACGTTTGTTAGCTAAGTTAGGAGCAATAGTGACAGTTAATGATGGCAAACCATTTGATGAAAATCCAACAGCACAGTCTTTGTTGG
AAGAGGGTATTAAAGTGGTTTGTGGTAGTCATCCTTTAGAATTGTTAGATGAGGATTTTTGTTACATGATTAAAAATCCAGGAATA
CCTTATAACAATCCTATGGTCAAAAAAGCATTAGAAAAACAAATCCCTGTTTTGACTGAAGTGGAATTAGCATACTTAGTTTCAGA
ATCTCAGCTAATAGGTATTACAGGCTCTAACGGGAAAACGACAACGACAACGATGATTGCAGAAGTCTTAAATGCTGGAGGTCAGA
GAGGTTTGTTAGCTGGGAATATCGGCTTTCCTGCTAGTGAAGTTGTTCAGGCTGCGAATGATAAAGATACTCTAGTTATGGAATTA
TCAAGTTTTCAGCTAATGGGAGTTAAGGAATTTCGTCCTCATATTGCAGTAATTACTAATTTAATGCCAACTCATTTAGATTATCA
TGGGTCTTTTGAAGATTATGTTGCTGCAAAATGGAATATCCAAAATCAAATGTCTTCATCTGATTTTTTGGTACTTAATTTTAATC
AAGGTATTTCTAAAGAGTTAGCTAAAACTACTAAAGCAACAATCGTTCCTTTCTCTACTACGGAAAAAGTTGATGGTGCTTACGTA
CAAGACAAGCAACTTTTCTATAAAGGGGAGAATATTATGTCAGTAGATGACATTGGTGTCCCAGGAAGCCATAACGTAGAGAATGC
TCTAGCAACTATTGCGGTTGCTAAACTGGCTGGTATCAGTAATCAAGTTATTAGAGAAACTTTAAGCAATTTTGGAGGTGTTAAAC
ACCGCTTGCAATCACTCGGTAAGGTTCATGGTATTAGTTTCTATAACGACAGCAAGTCAACTAATATATTGGCAACTCAAAAAGCA
TTATCTGGCTTTGATAATACTAAAGTTATCCTAATTGCAGGAGGTCTTGATCGCGGTAATGAGTTTGATGAATTGATACCAGATAT
CACTGGACTTAAACATATGGTTGTTTTAGGGGAATCGGCATCTCGAGTAAAACGTGCTGCACAAAAAGCAGGAGTAACTTATAGCG
ATGCTTTAGATGTTAGAGATGCGGTACATAAAGCTTATGAGGTGGCACAACAGGGCGATGTTATCTTGCTAAGTCCTGCAAATGCA
TCATGGGACATGTATAAGAATTTCGAAGTCCGTGGTGATGAATTCATTGATACTTTCGAAAGTCTTAGAGGAGAG

SEQ ID NO. 14

MGRVMKTITTFENKKVLVLGLARSGEAAARLLAKLGAIVTVNDGKPFDENPTAQSLLEEGIKVVCGSHPLELLDEDFCYMIKNPGI
PYNNPMVKKALEKQIPVLTEVELAYLVSESQLIGITGSNGKTTTTTMIAEVLNAGGQRGLLAGNIGFPASEVVQAANDKDTLVMEL
SSFQLMGVKEFRPHIAVITNLMPTHLDYHGSFEDYVAAKWNIQNQMSSSDFLVLNFNQGISKELAKTTKATIVPFSTTEKVDGAYV
QDKQLFYKGENIMSVDDIGVPGSHNVENALATIAVAKLAGISNQVIRETLSNFGGVKHRLQSLGKVHGISFYNDSKSTNILATQKA
LSGFDNTKVILIAGGLDRGNEFDELIPDITGLKHMVVLGESASRVKRAAQKAGVTYSDALDVRDAVHKAYEVAQQGDVILLSPANA
SWDMYKNFEVRGDEFIDTFESLRGE

The nucleotide and amino acid sequences of GBS 313 are in Ref. 3 are SEQ ID 4089 and SEQ ID 4090. These sequences are set forth as SEQ ID NOS 15 and 16 below:

SEQ ID NO. 15

ATGAAACGTATTGCTGTTTTAACTAGTGGTGGTGACGCCCCTGGTATGAACGCTGCTATCCGTGCAGTTGTTCGTAAAGCAATTTCTGAAGGTATG
GAAGTTTACGGCATCAACCAAGGTTACTATGGTATGGTGACAGGGGATATTTTCCCTTTGGATGCTAATTCTGTTGGGGATACTATCAACCGTGGA
GGAACGTTTTTACGTTCAGCACGTTATCCTGAATTTGCTGAACTTGAAGGTCAGCTTAAAGGGATTGAACAGCTTAAAAAACACGGTATTGAAGGT
GTAGTAGTTATCGGTGGTGATGGTTCTTATCATGGTGCTATGCGTCTAACTGAGCACGGTTTCCCAGCTGTTGGTTTGCCGGGTACAATTGATAAC
GATATCGTTGGCACTGACTATACTATTGGTTTTGACACAGCAGTTGCGACAGCAGTTGAGAATCTTGACCGTCTTCGTGATACATCAGCAAGTCAT
AACCGTACTTTTGTTGTTGAGGTTATGGGAAGAAATGCAGGAGATATCGCTCTTTGGTCAGGTATCGCTGCAGGTGCAGATCAAATTATTGTTCCT
GAAGAAGAGTTCAATATTGATGAAGTTGTCTCAAATGTTAGAGCTGGCTATGCAGCTGGTAAACATCACCAAATCATCGTCCTTGCAGAAGGTGTT
ATGAGTGGTGATGAGTTTGCAAAAACAATGAAAGCAGCAGGAGACGATAGCGATCTTCGTGTGACGAATTTAGGACATCTGCTCCGTGGTGGTAGT
CCGACGGCTCGTGATCGTGTCTTAGCATCTCGTATGGGAGCGTACGCTGTTCAATTGTTGAAAGAAGGTCGTGGTGGTTTAGCCGTTGGTGTCCAC
AACGAAGAAATGGTTGAAAGTCCAATTTTAGGTTTAGCAGAAGAAGGTGCTTTGTTCAGCTTGACTGATGAAGGAAAAATCGTTGTTAATAATCCG
CATAAAGCGGACCTTCGCTTGGCAGCACTTAATCGTGACCTTGCCAACCAAAGTAGTAAA

SEQ ID NO. 16

MKRIAVLTSGGDAPGMNAAIRAVVRKAISEGMEVYGINQGYYGMVTGDIFPLDANSVGDTINRGGTFLRSARYPEFAELEGQLKGIEQLKKHGIEG
VVVIGGDGSYHGAMRLTEHGFPAVGLPGTIDNDIVGTDYTIGFDTAVATAVENLDRLRDTSASHNRTFVVEVMGRNAGDIALWSGIAAGADQIIVP
EEEFNIDEVVSNVRAGYAAGKHHQIIVLAEGVMSGDEFAKTMKAAGDDSDLRVTNLGHLLRGGSPTARDRVLASRMGAYAVQLLKEGRGGLAVGVH
NEEMVESPILGLAEEGALFSLTDEGKIVVNNPHKADLRLAALNRDLANQSSK

The nucleotide and amino acid sequences of GBS 322 in Ref. 3 are SEQ ID 8539 and SEQ ID 8540. These sequences are set forth below as SEQ ID NOS 17 and 18:

SEQ ID NO. 17

ATGAATAAAAAGGTACTATTGACATCGACAATGGCAGCTTCGCTATTATCAGTCGCAAGTGTTCAAGCACAAGAAACAGATACGACGTGGACAGCA
CGTACTGTTTCAGAGGTAAAGGCTGATTTGGTAAAGCAAGACAATAAATCATCATATACTGTGAAATATGGTGATACACTAAGCGTTATTTCAGAA
GCAATGTCAATTGATATGAATGTCTTAGCAAAAATAAATAACATTGCAGATATCAATCTTATTTATCCTGAGACAACACTGACAGTAACTTACGAT
CAGAAGAGTCATACTGCCACTTCAATGAAAATAGAAACACCAGCAACAAATGCTGCTGGTCAAACAACAGCTACTGTGGATTTGAAAACCAATCAA
GTTTCTGTTGCAGACCAAAAAGTTTCTCTCAATACAATTTCGGAAGGTATGACACCAGAAGCAGCAACAACGATTGTTTCGCCAATGAAGACATAT
TCTTCTGCGCCAGCTTTGAAATCAAAAGAAGTATTAGCACAAGAGCAAGCTGTTAGTCAAGCAGCAGCTAATGAACAGGTATCACCAGCTCCTGTG
AAGTCGATTACTTCAGAAGTTCCAGCAGCTAAAGAGGAAGTTAAACCAACTCAGACGTCAGTCAGTCAGTCAACAACAGTATCACCAGCTTCTGTT
GCCGCTGAAACACCAGCTCCAGTAGCTAAAGTAGCACCGGTAAGAACTGTAGCAGCCCCTAGAGTGGCAAGTGTTAAAGTAGTCACTCCTAAAGTA
GAAACTGGTGCATCACCAGAGCATGTATCAGCTCCAGCAGTTCCTGTGACTACGACTTCACCAGCTACAGACAGTAAGTTACAAGCGACTGAAGTT
AAGAGCGTTCCGGTAGCACAAAAAGCTCCAACAGCAACACCGGTAGCACAACCAGCTTCAACAACAAATGCAGTAGCTGCACATCCTGAAAATGCA
GGGCTCCAACCTCATGTTGCAGCTTATAAAGAAAAAGTAGCGTCAACTTATGGAGTTAATGAATTCAGTACATACCGTGCGGGAGATCCAGGTGAT
CATGGTAAAGGTTTAGCAGTTGACTTTATTGTAGGTACTAATCAAGCACTTGGTAATAAAGTTGCACAGTACTCTACACAAAATATGGCAGCAAAT
AACATTTCATATGTTATCTGGCAACAAAAGTTTTACTCAAATACAAACAGTATTTATGGACCTGCTAATACTTGGAATGCAATGCCAGATCGTGGT
GGCGTTACTGCCAACCACTATGACCACGTTCACGTATCATTTAACAAATAATATAAAAAAGGAAGCTATTTGGCTTCTTTTTTATATGCCTTGAAT
AGACTTTCAAGGTTCTTATATAATTTTTATTA

SEQ ID NO. 18

MNKKVLLTSTMAASLLSVASVQAQETDTTWTARTVSEVKADLVKQDNKSSYTVKYGDTLSVISEAMSIDMNVLAKINNIADINLIYPETTLTVTYD
QKSHTATSMKIETPATNAAGQTTATVDLKTNQVSVADQKVSLNTISEGMTPEAATTIVSPMKTYSSAPALKSKEVLAQEQAVSQAAANEQVSPAPV
KSITSEVPAAKEEVKPTQTSVSQSTTVSPASVAAETPAPVAKVAPVRTVAAPRVASVKVVTPKVETGASPEHVSAPAVPVTTTSPATDSKLQATEV
KSVPVAQKAPTATPVAQPASTTNAVAAHPENAGLQPHVAAYKEKVASTYGVNEFSTYRAGDPGDHGKGLAVDFIVGTNQALGNKVAQYSTQNMAAN
NISYVIWQQKFYSNTNSIYGPANTWNAMPDRGGVTANHYDHVHVSFNK

The nucleotide and amino acid sequences of GBS 328 in Ref. 3 are SEQ ID 6015 and SEQ ID 6016. These sequences are set forth below as SEQ ID NOS 19 and 20:

SEQ ID NO. 19

ATGAAAAAGAAAATTATTTTGAAAAGTAGTGTTCTTGGTTTAGTCGCTGGGACTTCTATTATGTTCTCAAGCGTGTTCGCGGACCAAGTCGGTGTC
CAAGTTATAGGCGTCAATGACTTTCATGGTGCACTTGACAATACTGGAACAGCAAATATGCCTGATGGAAAAGTTGCTAATGCTGGTACTGCTGCT
CAATTAGATGCTTATATGGATGACGCTCAAAAAGATTTCAAACAAACTAACCCTAATGGTGAAAGCATTAGGGTTCAAGCAGGCGATATGGTTGGA
GCAAGTCCAGCCAACTCTGGGCTTCTTCAAGATGAACCAACTGTCAAAAATTTTAATGCAATGAATGTTGAGTATGGCACATTGGGTAACCATGAA
TTTGATGAAGGGTTGGCAGAATATAATCGTATCGTTACTGGTAAAGCCCCTGCTCCAGATTCTAATATTAATAATATTACGAAATCATACCCACAT
GAAGCTGCAAAACAAGAAATTGTAGTGGCAAATGTTATTGATAAAGTTAACAAACAAATTCCTTACAATTGGAAGCCTTACGCTATTAAAAATATT
CCTGTAAATAACAAAAGTGTGAACGTTGGCTTTATCGGGATTGTCACCAAAGACATCCCAAACCTTGTCTTACGTAAAAATTATGAACAATATGAA
TTTTTAGATGAAGCTGAAACAATCGTTAAATACGCCAAAGAATTACAAGCTAAAAATGTCAAAGCTATTGTAGTTCTCGCACATGTACCTGCAACA
AGTAAAAATGATATTGCTGAAGGTGAAGCAGCAGAAATGATGAAAAAAGTCAATCAACTCTTCCCTGAAAATAGCGTAGATATTGTCTTTGCTGGA
CACAATCATCAATATACAAATGGTCTTGTTGGTAAAACTCGTATTGTACAAGCGCTCTCTCAAGGAAAAGCCTATGCTGATGTACGTGGTGTCTTA
GATACTGATACACAAGATTTCATTGAGACCCCTTCAGCTAAAGTAATTGCAGTTGCTCCTGGTAAAAAAACAGGTAGTGCCGATATTCAAGCCATT
GTTGACCAAGCTAATACTATCGTTAAACAAGTAACAGAAGCTAAAATTGGTACTGCCGAGGTAAGTGTCATGATTACGCGTTCTGTTGATCAAGAT
AATGTTAGTCCGGTAGGCAGCCTCATCACAGAGGCTCAACTAGCAATTGCTCGAAAAAGCTGGCCAGATATCGATTTTGCCATGACAAATAATGGT
GGCATTCGTGCTGACTTACTCATCAAACCAGATGGAACAATCACCTGGGGAGCTGCACAAGCAGTTCAACCTTTTGGTAATATCTTACAAGTCGTC
GAAATTACTGGTAGAGATCTTTATAAAGCACTCAACGAACAATACGACCAAAAACAAAATTTCTTCCTTCAAATAGCTGGTCTGCGATACACTTAC
ACAGATAATAAAGAGGGCGGGGAAGAAACACCATTTAAAGTTGTAAAAGCTTATAAATCAAATGGTGAGGAAATCAATCCTGATGCAAAATACAAA
TTAGTTATCAATGACTTTTTATTCGGTGGTGGTGATGGCTTTGCAAGCTTCAGAAATGCCAAACTTCTAGGAGCCATTAACCCCGATACAGAGGTA
TTTATGGCCTATATCACTGATTTAGAAAAAGCTGGTAAAAAAGTGAGCGTTCCAAATAATAAACCTAAAATCTATGTCACTATGAAGATGGTTAAT
GAAACTATTACACAAAATGATGGTACACATAGCATTATTAAGAAACTTTATTTAGATCGACAAGGAAATATTGTAGCACAAGAGATTGTATCAGAC

ACTTTAAACCAAACAAAATCAAAATCTACAAAAATCAACCCTGTAACTACAATTCACAAAAAACAATTACACCAATTTACAGCTATTAACCCTATG
AGAAATTATGGCAAACCATCAAACTCCACTACTGTAAAATCAAAACAATTACCAAAAACAAACTCTGAATATGGACAATCATTCCTTATGTCTGTC
TTTGGTGTTGGACTTATAGGAATTGCTTTAAATACAAAGAAAAAACATATGAAA

SEQ ID NO. 20

MKKKIILKSSVLGLVAGTSIMFSSVFADQVGVQVIGVNDFHGALDNTGTANMPDGKVANAGTAAQLDAYMDDAQKDFKQTNPNGESIRVQAGDMVG
ASPANSGLLQDEPTVKNFNAMNVEYGTLGNHEFDEGLAEYNRIVTGKAPAPDSNINNITKSYPHEAAKQEIVVANVIDKVNKQIPYNWKPYAIKNI
PVNNKSVNVGFIGIVTKDIPNLVLRKNYEQYEFLDEAETIVKYAKELQAKNVKAIVVLAHVPATSKNDIAEGEAAEMMKKVNQLFPENSVDIVFAG
HNHQYTNGLVGKTRIVQALSQGKAYADVRGVLDTDTQDFIETPSAKVIAVAPGKKTGSADIQAIVDQANTIVKQVTEAKIGTAEVSVMITRSVDQD
NVSPVGSLITEAQLAIARKSWPDIDFAMTNNGGIRADLLIKPDGTITWGAAQAVQPFGNILQVVEITGRDLYKALNEQYDQKQNFFLQIAGLRYTY
TDNKEGGEETPFKVVKAYKSNGEEINPDAKYKLVINDFLFGGGDGFASFRNAKLLGAINPDTEVFMAYITDLEKAGKKVSVPNNKPKIYVTMKMVN
ETITQNDGTHSIIKKLYLDRQGNIVAQEIVSDTLNQTKSKSTKINPVTTIHKKQLHQFTAINPMRNYGKPSNSTTVKSKQLPKTNSEYGQSFLMSV
FGVGLIGIALNTKKKHMK

The nucleotide and amino acid sequences of GBS 330 in Ref. 3 are SEQ ID 8791 and SEQ ID 8792. These sequences are set forth below as SEQ ID NOS 21 and 22:

SEQ ID NO. 21

ATGAATAAACGCGTAAAAATCGTTGCAACACTTGGTCCTGCGGTTGAATTCCGTGGTGGTAAGAAGTTTGGTGAGTCTGGATACTGGGGTGAAAGC
CTTGACGTAGAAGCTTCAGCAGAAAAAATTGCTCAATTGATTAAAGAAGGTGCTAACGTTTTCCGTTTCAACTTCTCACATGGAGATCATGCTGAG
CAAGGAGCTCGTATGGCTACTGTTCGTAAAGCAGAAGAGATTGCAGGACAAAAAGTTGGCTTCCTCCTTGATACTAAAGGACCTGAAATTCGTACA
GAACTTTTTGAAGATGGTGCAGATTTCCATTCATATACAACAGGTACAAAATTACGTGTTGCTACTAAGCAAGGTATCAAATCAACTCCAGAAGTG
ATTGCATTGAATGTTGCTGGTGGACTTGACATCTTTGATGACGTTGAAGTTGGTAAGCAAATCCTTGTTGATGATGGTAAACTAGGTCTTACTGTG
TTTGCAAAAGATAAAGACACTCGTGAATTTGAAGTAGTTGTTGAGAATGATGGCCTTATTGGTAAACAAAAAGGTGTAAACATCCCTTATACTAAA
ATTCCTTTCCCAGCACTTGCAGAACGCGATAATGCTGATATCCGTTTTGGACTTGAGCAAGGACTTAACTTTATTGCTATCTCATTTGTACGTACT
GCTAAAGATGTTAATGAAGTTCGTGCTATTTGTGAAGAAACTGGSMATGGACACGTTAAGTTGTTTGCTAAAATTGAAAATCAACAAGGTATCGAT
AATATTGATGAGATTATCGAAGCAGCAGATGGTATTATGATTGCTCGTGGTGATATGGGTATCGAAGTTCCATTTGAAATGGTTCCAGTTTACCAA
AAAATGATCATTACTAAAGTTAATGCAGCTGGTAAAGCAGTTATTACAGCAACAAATATGCTTGAAACAATGACTGATAAACCACGTGCGACTCGT
TCAGAAGTATCTGATGTCTTCAATGCTGTTATTGATGGTACTGATGCTACAATGCTTTCAGGTGAGTCAGCTAATGGTAAATACCCAGTTGAGTCA
GTTCGTACAATGGCTACTATTGATAAAAATGCTCAAACATTACTCAATGAGTATGGTCGCTTAGACTCATCTGCATTCCCACGTAATAACAAAACT
GATGTTATTGCATCTGCGGTTAAAGATGCAACACACTCAATGGATATCAAACTTGTTGTAACAATTACTGAAACAGGTAATACAGCTCGTGCCATT
TCTAAATTCCGTCCAGATGCAGACATTTTGGCTGTTACATTTGATGAAAAAGTACAACGTTCATTGATGATTAACTGGGGTGTTATCCCTGTCCTT
GCAGACAAACCAGCATCTACAGATGATATGTTTGAGGTTGCAGAACGTGTAGCACTTGAAGCAGGATTTGTTGAATCAGGCGATAATATCGTTATC
GTTGCAGGTGTTCCTGTAGGTACAGGTGGAACTAACACAATGCGTGTTCGTACTGTTAAA

SEQ ID NO. 22

MNKRVKIVATLGPAVEFRGGKKFGESGYWGESLDVEASAEKIAQLIKEGANVFRFNFSHGDHAEQGARMATVRKAEEIAGQKVGFLLDTKGPEIRT
ELFEDGADFHSYTTGTKLRVATKQGIKSTPEVIALNVAGGLDIFDDVEVGKQILVDDGKLGLTVFAKDKDTREFEVVVENDGLIGKQKGVNIPYTK
IPFPALAERDNADIRFGLEQGLNFIAISFVRTAKDVNEVRAICEETGXGHVKLFAKIENQQGIDNIDEIIEAADGIMIARGDMGIEVPFEMVPVYQ
KMIITKVNAAGKAVITATNMLETMTDKPRATRSEVSDVFNAVIDGTDATMLSGESANGKYPVESVRTMATIDKNAQTLLNEYGRLDSSAFPRNNKT
DVIASAVKDATHSMDIKLVVTITETGNTARAISKFRPDADILAVTFDEKVQRSLMINWGVIPVLADKPASTDDMFEVAERVALEAGFVESGDNIVI
VAGVPVGTGGTNTMRVRTVK

The nucleotide and amino acid sequences of GBS 338 in Ref. 3 are SEQ ID 8637 and SEQ ID 8638. These sequences are set forth below as SEQ ID NOS 23 and 24:

SEQ ID NO. 23

TTGTCTGCTATAATAGACAAAAAGGTGGTGATATTTATGTATTTAGCATTAATCGGTGATATCATTAATTCAAAACAGATACTTGA
ACGTGAAACTTTCCAACAGTCTTTTCAGCAACTAATGACCGAACTATCTGATGTATATGGTGAAGAGCTGATTTCTCCATTCACTA
TTACAGCTGGTGATGAATTTCAAGCTTTATTGAAACCATCAAAAAAGGTATTTCAAATTATTGACCATATTCAACTAGCTCTAAAA
CCTGTTAATGTAAGGTTCGGCCTCGGTACAGGAAACATTATAACATCCATCAATTCAAATGAAAGTATCGGTGCTGATGGTCCTGC
CTACTGGCATGCTCGCTCAGCTATTAATCATATACATGATAAAAATGATTATGGAACAGTTCAAGTAGCTATTTGCCTTGATGATG
AAGACCAAAACCTTGAATTAACACTAAATAGTCTCATTTCAGCTGGTGATTTTATCAAGTCAAAATGGACTACAAACCATTTTCAA
ATGCTTGAGCACTTAATACTTCAAGATAATTATCAAGAACAATTTCAACATCAAAAGTTAGCCCAACTGGAAAATATTGAACCTAG
TGCGCTGACTAAACGCCTTAAAGCAAGCGGTCTGAAGATTTACTTAAGAACGAGAACACAGGCAGCCGATCTATTAGTTAAAAGTT
GCACTCAAACTAAAGGGGGAAGCTATGATTTC

SEQ ID NO. 24

MSAIIDKKVVIFMYLALIGDIINSKQILERETFQQSFQQLMTELSDVYGEELISPFTITAGDEFQALLKPSKKVFQIIDHIQLALKPVNVRFGLGTG
NIITSINSNESIGADGPAYWHARSAINHIHDKNDYGTVQVAICLDDEDQNLELTLNSLISAGDFIKSKWTTNHFQMLEHLILQDNYQEQFQHQKLAQ
LENIEPSALTKRLKASGLKIYLRTRTQAADLLVKSCTQTKGGSYDF

The nucleotide and amino acid sequences of GBS 358 in Ref. 3 are SEQ ID 3183 and SEQ ID 3184. These sequences are set forth below as SEQ ID NOS 25 and 26:

SEQ ID NO. 25

ATGTTTTATACAATTGAAGAGCTGGTAGAGCAAGCTAATAGCCAACATAAGGGTAACATAGCAGAGCTCATGATCCAAACGGAAATTGAAATGACT
GGTAGAAGTCGTGAAGAAATTCGTTATATTATGTCCCGAAATCTTGAAGTCATGAAAGCTTCTGTTATTGATGGATTAACCCCTAGTAAATCAATC
AGTGGTTTAACAGGCGGTGATGCTGTCAAGATGGATCAATATTTACAATCAGGAAAAACTATTTCAGATACCACAATCCTAGCTGCCGTTAGGAAT
GCTATGGCTGTTAATGAGTTAAATGCTAAGATGGGACTGGTCTGTGCAACACCAACTGCAGGTAGTGCAGGATGTTTACCAGCTGTGATTTCTACA
GCCATTGAAAAGCTTAATTTAACAGAAGAAGAGCAACTTGATTTTCTATTTACAGCCGGCGCATTTGGTCTCGTCATTGGTAATAATGCCTCTATC
TCAGGTGCAGAAGGAGGTTGCCAAGCTGAAGTTGGGTCAGCTAGTGCTATGGCTGCGGCTGCTTTAGTTATGGCTGCTGGAGGTACTCCTTTCCAA
GCTAGCCAAGCTATAGCATTTGTTATTAAAAATATGCTTGGACTTATCTGTGACCCTGTTGCAGGTTTAGTTGAAGTCCCTTGTGTGAAGCGGAAT
GCTCTTGGATCAAGTTTTGCACTTGTTGCTGCTGATATGGCCTTGGCTGGTATTGAATCGCAAATTCCAGTAGATGAAGTTATTGATGCAATGTAT
CAAGTTGGATCAAGTTTACCGACTGCTTTTCGTGAGACTGCAGAAGGAGGACTTGCTGCCACGCCGACAGGAAGACGTTATAGTAAAGAAATTTTT
GGGGAA

SEQ ID NO. 26

MFYTIEELVEQANSQHKGNIAELMIQTEIEMTGRSREEIRYIMSRNLEVMKASVIDGLTPSKSISGLTGGDAVKMDQYLQSGKTISDTTILAAVRN
AMAVNELNAKMGLVCATPTAGSAGCLPAVISTAIEKLNLTEEEQLDFLFTAGAFGLVIGNNASISGAEGGCQAEVGSASAMAAAALVMAAGGTPFQ
ASQAIAFVIKNMLGLICDPVAGLVEVPCVKRNALGSSFALVAADMALAGIESQIPVDEVIDAMYQVGSSLPTAFRETAEGGLAATPTGRRYSKEIF
GE

The nucleotide and amino acid sequences of GBS 361 in Ref. 3 are SEQ ID 8769 and SEQ ID 8770. These sequences are set forth below as SEQ ID NOS 27 and 28:

SEQ ID NO. 27

ATGAGCGTATATGTTAGTGGAATAGGAATTATTTCTTCTTTGGGAAAGAATTATAGCGAGCATAAACAGCATCTCTTCGACTTAAAAGAAGGAATTT
CTAAACATTTATATAAAAATCACGACTCTATTTTAGAATCTTATACAGGAAGCATAACTAGTGACCCAGAGGTTCCTGAGCAATACAAAGATGAGAC
ACGTAATTTTAAATTTGCTTTTACCGCTTTTGAAGAGGCTCTTGCTTCTTCAGGTGTTAATTTAAAAGCTTATCATAATATTGCTGTGTGTTTAGGG
ACCTCACTTGGGGGAAAGAGTGCTGGTCAAAATGCCTTGTATCAATTTGAAGAAGGAGAGCGTCAAGTAGATGCTAGTTTATTAGAAAAAGCATCTG
TTTACCATATTGCTGATGAATTGATGGCTTATCATGATATTGTGGGAGCTTCGTATGTTATTTCAACCGCCTGTTCTGCAAGTAATAATGCCGTAAT
ATTAGGAACACAATTACTTCAAGATGGCGATTGTGATTTAGCTATTTGTGGTGGCTGTGATGAGTTAAGTGATATTTCTTTAGCAGGCTTCACATCA
CTAGGAGCTATTAATACAGAAATGGCATGTCAGCCCTATTCTTCTGGAAAAGGAATCAATTTGGGTGAGGGCGCTGGTTTTGTTGTTCTTGTCAAAG
ATCAGTCCTTAGCTAAATATGGAAAAATTATCGGTGGTCTTATTACTTCAGATGGTTATCATATAACAGCACCTAAGCCAACAGGTGAAGGGGCGGC
ACAGATTGCAAAGCAGCTAGTGACTCAAGCAGGTATTGACTACAGTGAGATTGACTATATTAACGGTCACGGTACAGGTACTCAAGCTAATGATAAA
ATGGAAAAAAATATGTATGGTAAGTTTTTCCCGACAACGACATTGATCAGCAGTACCAAGGGGCAAACGGGTCATACTCTAGGGGCTGCAGGTATTA
TCGAATTGATTAATTGTTTAGCGGCAATAGAGGAACAGACTGTACCAGCAACTAAAAATGAGATTGGGATAGAAGGTTTTCCAGAAAATTTTGTCTA
TCATCAAAAGAGAGAATACCCAATAAGAAATGCTTTAAATTTTTCGTTTGCTTTTGGTGGAAATAATAGTGGTGTCTTATTGTCATCTTTAGATTCA
CCTCTAGAAACATTACCTGCTAGAGAAAATCTTAAAATGGCTATCTTATCATCTGTTGCTTCCATTTCTAAGAATGAATCACTTTCTATAACCTATG
AAAAAGTTGCTAGTAATTTCAACGACTTTGAAGCATTACGCTTTAAAGGGGCTAGACCACCCAAAACTGTCAACCCAGCACAATTTAGGAAAATGGA
TGATTTTTCCAAAATGGTTGCCGTAACAACAGCTCAAGCACTAATAGAAAGCAATATTAATCTAAAAAAACAAGATACTTCAAAAGTAGGAATTGTA
TTTACAACACTTTCTGGACCAGTTGAGGTTGTTGAAGGTATTGAAAAGCAAATCACAACAGAAGGATATGCACATGTTTCTGCTTCACGATTCCCGT
TTACAGTAATGAATGCAGCAGCTGGTATGCTTTCTATCATTTTTAAAATAACAGGTCCTTTATCTGTCATTTCGACAAATAGTGGAGCGCTTGATGG
TATACAATATGCCAAGGAAATGATGCGTAACGATAATCTAGACTATGTGATTCTTGTTTCTGCTAATCAGTGGACAGACATGAGTTTTATGTGGTGG
CAACAATTAAACTATGATAGTCAAATGTTTGTCGGTTCTGATTATTGTTCAGCACAAGTCCTCTCTCGTCAAGCATTGGATAATTCTCCTATAATAT
TAGGTAGTAAACAATTAAAATATAGCCATAAAACATTCACAGATGTGATGACTATTTTTGATGCTGCGCTTCAAAATTTATTATCAGACTTAGGACT
AACCATAAAAGATATCAAAGGTTTCGTTTGGAATGAGCGGAAGAAGGCAGTTAGTTCAGATTATGATTTCTTAGCGAACTTGTCTGAGTATTATAAT
ATGCCAAACCTTGCTTCTGGTCAGTTTGGATTTTCATCTAATGGTGCTGGTGAAGAACTGGACTATACTGTTAATGAAAGTATAGAAAAGGGCTATT
ATTTAGTCCTATCTTATTCGATCTTCGGTGGTATCTCTTTTGCTATTATTGAAAAAAGG

SEQ ID NO. 28

MSVYVSGIGIISSLGKNYSEHKQHLFDLKEGISKHLYKNHDSILESYTGSITSDPEVPEQYKDETRNFKFAFTAFEEALASSGVNLKAYHNIAVCLG
TSLGGKSAGQNALYQFEEGERQVDASLLEKASVYHIADELMAYHDIVGASYVISTACSASNNAVILGTQLLQDGDCDLAICGGCDELSDISLAGFTS
LGAINTEMACQPYSSGKGINLGEGAGFVVLVKDQSLAKYGKIIGGLITSDGYHITAPKPTGEGAAQIAKQLVTQAGIDYSEIDYINGHGTGTQANDK
MEKNMYGKFFPTTTLISSTKGQTGHTLGAAGIIELINCLAAIEEQTVPATKNEIGIEGFPENFVYHQKREYPIRNALNFSFAFGGNNSGVLLSSLDS
PLETLPARENLKMAILSSVASISKNESLSITYEKVASNFNDFEALRFKGARPPKTVNPAQFRKMDDFSKMVAVTTAQALIESNINLKKQDTSKVGIV
FTTLSGPVEVVEGIEKQITTEGYAHVSASRFPFTVMNAAAGMLSIIFKITGPLSVISTNSGALDGIQYAKEMMRNDNLDYVILVSANQWTDMSFMWW
QQLNYDSQMFVGSDYCSAQVLSRQALDNSPIILGSKQLKYSHKTFTDVMTIFDAALQNLLSDLGLTIKDIKGFVWNERKKAVSSDYDFLANLSEYYN
MPNLASGQFGFSSNGAGEELDYTVNESIEKGYYLVLSYSIFGGISFAIIEKR

The nucleotide and amino acid sequences of GBS 404 in Ref. 3 are SEQ ID 8799 and SEQ ID 8800. These sequences are set forth below as SEQ ID NOS 29 and 30:

SEQ ID NO. 29

ATGAAAATAGATGACCTAAGAAAAAGCGACAATGTTGAAGATCGTCGCTCCAGTAGCGGAGGTTCATTCTCTAGCGGAGGAAGTGGATTACCGATT
CTTCAACTTTTATTGCTGCGAGGGAGTTGGAAAACCAAGCTTGTGGTTTTAATCATCTTACTGCTACTTGGCGGAGGGGGACTAACCAGCATTTTT
AATGACTCATCCTCACCTTCTAGTTACCAATCTCAGAATGTCTCACGTTCTGTTGATAATAGCGCAACGAGAGAACAAATCGATTTCGTTAATAAA
GTCCTTGGCTCAACTGAGGATTTCTGGTCACAAGAATTCCAAACCCAAGGTTTTGGAAATTATAAGGAACCAAAACTTGTTCTTTACACCAATTCA
ATTCAAACAGGTTGTGGTATAGGTGAATCTGCTTCAGGACCATTTTATTGTTCAGCAGATAAAAAAATCTATCTTGATATTTCTTTTTACAATGAA
TTATCACATAAATATGGTGCTACTGGTGATTTTGCTATGGCCTACGTCATCGCCCACGAAGTTGGTCACCACATTCAAACAGAGTTAGGCATTATG
GATAAGTATAATAGAATGCGACACGGACTTACTAAGAAAGAAGCAAATGCTTTAAATGTTCGGCTAGAACTTCAAGCAGATTATTATGCAGGGGTA
TGGGCTCACTACATCAGGGGAAAAAATCTCTTAGAACAAGGAGACTTTGAAGAGGCCATGAATGCTGCCCACGCCGTCGGAGACGATACCCTTCAG
AAAGAAACCTACGGAAAATTAGTGCCTGATAGCTTTACCCATGGAACAGCTGAACAACGCCAACGTTGGTTTAACAAAGGCTTTCAATATGGTGAC
ATCCAACACGGTGATACTTTCTCCGTAGAACATCTA

SEQ ID NO. 30

MKIDDLRKSDNVEDRRSSSGGSFSSGGSGLPILQLLLLRGSWKTKLVVLIILLLLGGGGLTSIFNDSSSPSSYQSQNVSRSVDNSATREQIDFVNK
VLGSTEDFWSQEFQTQGFGNYKEPKLVLYTNSIQTGCGIGESASGPFYCSADKKIYLDISFYNELSHKYGATGDFAMAYVIAHEVGHHIQTELGIM
DKYNRMRHGLTKKEANALNVRLELQADYYAGVWAHYIRGKNLLEQGDFEEAMNAAHAVGDDTLQKETYGKLVPDSFTHGTAEQRQRWFNKGFQYGD
IQHGDTFSVEHL

The nucleotide and amino acid sequences of GBS 656 in Ref. 3 are SEQ ID 9323 and SEQ ID 9324. These sequences are set forth below as SEQ ID NOS 31 and 32:

SEQ ID NO. 31

ATGAAAAGATTACATAAACTGTTTATAACCGTAATTGCTACATTAGGTATGTTGGGGGTAATGACCTTTGGTCTTCCAACGCAGCCGCAAAACGTA
ACGCCGATAGTACATGCTGATGTCAATTCATCTGTTGATACGAGCCAGGAATTTCAAAATAATTTAAAAAATGCTATTGGTAACCTACCATTTCAA
TATGTTAATGGTATTTATGAATTAAATAATAATCAGACAAATTTAAATGCTGATGTCAATGTTAAAGCGTATGTTCAAAATACAATTGACAATCAA
CAAAGACTATCAACTGCTAATGCAATGCTTGATAGAACCATTCGTCAATATCAAAATCGCAGAGATACCACTCTTCCCGATGCAAATTGGAAACCA
TTAGGTTGGCATCAAGTAGCTACTAATGACCATTATGGACATGCAGTCGACAAGGGGCATTTAATTGCCTATGCTTTAGCTGGAAATTTCAAAGGT
TGGGATGCTTCCGTGTCAAATCCTCAAAATGTTGTCACACAAACAGCTCATTCCAACCAATCAAATCAAAAAATCAATCGTGGACAAAATTATTAT
GAAAGCTTAGTTCGTAAGGCGGTTGACCAAAACAAACGTGTTCGTTACCGTGTAACTCCATTGTACCGTAATGATACTGATTTAGTTCCATTTGCA
ATGCACCTAGAAGCTAAATCACAAGATGGCACATTAGAATTTAATGTTGCTATTCCAAACACACAAGCATCATACACTATGGATTATGCAACAGGA
GAAATAACACTAAAT

SEQ ID NO. 32

MKRLHKLFITVIATLGMLGVMTFGLPTQPQNVTPIVHADVNSSVDTSQEFQNNLKNAIGNLPFQYVNGIYELNNNQTNLNADVNVKAYVQNTIDNQ
QRLSTANAMLDRTIRQYQNRRDTTLPDANWKPLGWHQVATNDHYGHAVDKGHLIAYALAGNFKGWDASVSNPQNVVTQTAHSNQSNQKINRGQNYY
ESLVRKAVDQNKRVRYRVTPLYRNDTDLVPFAMHLEAKSQDGTLEFNVAIPNTQASYTMDYATGEITLN

The nucleotide and amino acid sequences of GBS 690 in Ref. 3 are SEQ ID 9965 and SEQ ID.9966. These sequences are set forth as SEQ ID NOS 33 and 34 below:

SEQ ID NO. 33

ATGAGTAAACGACAAAATTTAGGAATTAGTAAAAAAGGAGCAATTATATCAGGGCTCTCAGTGGCACTAATTGTAGTAATAGGTGGCTTTTTATGG
GTACAATCTCAACCTAATAAGAGTGCAGTAAAAACTAACTACAAAGTTTTTAATGTTAGAGAAGGAAGTGTTTCGTCCTCAACTCTTTTGACAGGA
AAAGCTAAGGCTAATCAAGAACAGTATGTGTATTTTGATGCTAATAAAGGTAATCGAGCAACTGTCACAGTTAAAGTGGGTGATAAAATCACAGCT
GGTCAGCAGTTAGTTCAATATGATACAACAACTGCACAAGCAGCCTACGACACTGCTAATCGTCAATTAAATAAAGTAGCGCGTCAGATTAATAAT
CTAAAGACAACAGGAAGTCTTCCAGCTATGGAATCAAGTGATCAATCTTCTTCATCATCACAAGGACAAGGGACTCAATCGACTAGTGGTGCGACG
AATCGTCTACAGCAAAATTATCAAAGTCAAGCTAATGCTTCATACAACCAACAACTTCAAGATTTGAATGATGCTTATGCAGATGCACAGGCAGAA
GTAAATAAAGCACAAAAAGCATTGAATGATACTGTTATTACAAGTGACGTATCAGGGACAGTTGTTGAAGTTAATAGTGATATTGATCCAGCTTCA
AAAACTAGTCAAGTACTTGTCCATGTAGCAACTGAAGGTAAACTCCAAGTACAAGGAACGATGAGTGAGTATGATTTGGCTAATGTTAAAAAAGAC
CAGGCTGTTAAAATAAAATCTAAGGTCTATCCTGACAAGGAATGGGAAGGTAAAATTTCATATATCTCAAATTATCCAGAAGCAGAAGCAAACAAC
AATGACTCTAATAACGGCTCTAGTGCTGTAAATTATAAATATAAAGTAGATATTACTAGCCCTCTCGATGCATTAAAACAAGGTTTTACCGTATCA
GTTGAAGTAGTTAATGGAGATAAGCACCTTATTGTCCCTACAAGTTCTGTGATAAACAAAGATAATAAACACTTTGTTTGGGTATACAATGATTCT
AATCGTAAAATTTCCAAAGTTGAAGTCAAAATTGGTAAAGCTGATGCTAAGACACAAGAAATTTTATCAGGTTTGAAAGCAGGACAAATCGTGGTT
ACTAATCCAAGTAAAACCTTCAAGGATGGGCAAAAAATTGATAATATTGAATCAATCGATCTTAACTCTAATAAGAAATCAGAGGTGAAA

SEQ ID NO. 34

MSKRQNLGISKKGAIISGLSVALIVVIGGFLWVQSQPNKSAVKTNYKVFNVREGSVSSSTLLTGKAKANQEQYVYFDANKGNRATVTVKVGDKITAG
QQLVQYDTTTAQAAYDTANRQLNKVARQINNLKTTGSLPAMESSDQSSSSSQGQGTQSTSGATNRLQQNYQSQANASYNQQLQDLNDAYADAQAEVN
KAQKALNDTVITSDVSGTVVEVNSDIDPASKTSQVLVHVATEGKLQVQGTMSEYDLANVKKDQAVKIKSKVYPDKEWEGKISYISNYPEAEANNNDS
NNGSSAVNYKYKVDITSPLDALKQGFTVSVEVVNGDKHLIVPTSSVINKDNKHFVWVYNDSNRKISKVEVKIGKADAKTQEILSGLKAGQIVVTNPS
KTFKDGQKIDNIESIDLNSNKKSEVK

The nucleotide and amino acid sequences of GBS 691 in Ref. 3 are SEQ ID 3691 and SEQ ID 3692. These sequences are set forth as SEQ ID NOS 35 and 36 below:

SEQ ID NO. 35

ATGAAAAAAAATTGGAATTATTGTCCTCACACTACTGACCTTCTTTTTGGTATCTTGCGGACAACAAACTAAACAAGAAAGCACTAAAACAACTATT
TCTAAAATGCCTAAAATTGAAGGCTTCACCTATTATGGAAAAATTCCTGAAAATCCGAAAAAAGTAATTAATTTTACATATTCTTACACTGGGTAT
TTATTAAAACTAGGTGTTAATGTTTCAAGTTACAGTTTAGACTTAGAAAAAGATAGCCCCGTTTTTGGTAAACAACTGAAAGAAGCTAAAAAATTA
ACTGCTGATGATACAGAAGCTATTGCCGCACAAAAACCTGATTTAATCATGGTTTTCGATCAAGATCCAAACATCAATACTCTGAAAAAAATTGCA
CCAACTTTAGTTATTAAATATGGTGCACAAAATTATTTAGATATGATGCCAGCCTTGGGGAAAGTATTCGGTAAAGAAAAAGAAGCTAATCAGTGG
GTTAGCCAATGGAAAACTAAAACTCTCGCTGTCAAAAAAGATTTACACCATATCTTAAAGCCTAACACTACTTTTACTATTATGGATTTTTATGAT
AAAAATATCTATTTATATGGTAATAATTTTGGACGCGGTGGAGAACTAATCTATGATTCACTAGGTTATGCTGCCCCAGAAAAAGTCAAAAAAGAT
GTCTTTAAAAAAGGGTGGTTTACCGTTTCGCAAGAAGCAATCGGTGATTACGTTGGAGATTATGCCCTTGTTAATATAAACAAAACGACTAAAAAA
GCAGCTTCATCACTTAAAGAAAGTGATGTCTGGAAGAATTTACCAGCTGTCAAAAAAGGGCACATCATAGAAAGTAACTACGACGTGTTTTATTTC
TCTGACCCTCTATCTTTAGAAGCTCAATTAAAATCATTTACAAAGGCTATCAAAGAAAATACAAAT

SEQ ID NO. 36

MKKIGIIVLTLLTFFLVSCGQQTKQESTKTTISKMPKIEGFTYYGKIPENPKKVINFTYSYTGYLLKLGVNVSSYSLDLEKDSPVF
GKQLKEAKKLTADDTEAIAAQKPDLIMVFDQDPNINTLKKIAPTLVIKYGAQNYLDMMPALGKVFGKEKEANQWVSQWKTKTLAVK
KDLHHILKPNTTFTIMDFYDKNIYLYGNNFGRGGELIYDSLGYAAPEKVKKDVFKKGWFTVSQEAIGDYVGDYALVNINKTTKKAA
SSLKESDVWKNLPAVKKGHIIESNYDVFYFSDPLSLEAQLKSFTKAIKENTN

Other preferred polypeptide antigens include: GBS4 (SEQ ID 2 from Ref. 3); GBS22 (SEQ ID 8584 from Ref. 3); and GBS85 (SEQ ID 216 from Ref. 3), including polypeptides having amino acid sequences with sequence identity thereto *etc.*

The polypeptide is preferably not a C protein (alpha or beta or epsilon) or a R protein (Rib).

The nucleotide and amino acid sequences of GBS 4 in Ref. 3 are SEQ ID 1 and SEQ ID 2. These sequences are set forth below as SEQ ID NOS 37 and 38:

SEQ ID NO. 37

ATGAAAGTGAAAAATAAGATTTTAACGATGGTAGCACTTACTGTCTTAACATGTGCTACTTATTCATCAATCGGTTATGCTGATACAAGTGATAAGA
ATACTGACACGAGTGTCGTGACTACGACCTTATCTGAGGAGAAAAGATCAGATGAACTAGACCAGTCTAGTACTGGTTCTTCTTCTGAAAATGAATC
GAGTTCATCAAGTGAACCAGAAACAAATCCGTCAACTAATCCACCTACAACAGAACCATCGCAACCCTCACCTAGTGAAGAGAACAAGCCTGATGGT
AGAACGAAGACAGAAATTGGCAATAATAAGGATATTTCTAGTGGAACAAAAGTATTAATTTCAGAAGATAGTATTAAGAATTTTAGTAAAGCAAGTA
GTGATCAAGAAGAAGTGGATCGCGATGAATCATCATCTTCAAAAGCAAATGATGGGAAAAAAGGCCACAGTAAGCCTAAAAAGGAACTTCCTAAAAC
AGGAGATAGCCACTCAGATACTGTAATAGCATCTACGGGAGGGATTATTCTGTTATCATTAAGTTTTTACAATAAGAAAATGAAACTTTAT

SEQ ID NO. 38

MKVKNKILTMVALTVLTCATYSSIGYADTSDKNTDTSVVTTTLSEEKRSDELDQSSTGSSSENESSSSSEPETNPSTNPPTTEPSQPSPSEENKPDG
RTKTEIGNNKDISSGTKVLISEDSIKNFSKASSDQEEVDRDESSSSKANDGKKGHSKPKKELPKTGDSHSDTVIASTGGIILLSLSFYNKKMKLY

The nucleotide and amino acid sequences of GBS 22 in Ref. 3 are SEQ 8583 and SEQ ID 8584. These sequences are set forth below as SEQ ID NOS 39 and 40:

SEQ ID NO. 39

ATGAAAAGGATACGGAAAAGCCTTATTTTTGTTCTCGGAGTAGTTACCCTAATTTGCTTATGTGCTTGTACTAAACAAAGCCAGCAAAAAAATGGCT
TGTCAGTAGTGACTAGCTTTTATCCAGTATATTCCATTACAAAAGCAGTTTCTGGTGATTTGAATGATATTAAAATGATTCGATCACAGTCAGGTAT
TCATGGTTTTGAACCCTCATCAAGTGATGTTGCTGCCATTTATGATGCTGATCTATTTCTTTATCATTCGCACACACTAGAAGCTTGGGCGAGACGT
TTGGAACCTAGTTTGCATCACTCTAAAGTATCTGTAATTGAAGCTTCAAAAGGTATGACTTTGGATAAAGTTCATGGCTTAGAAGATGTAGAGGCAG
AAAAAGGAGTAGATGAGTCAACCTTGTATGACCCTCACACTTGGAATGACCCTGTAAAAGTATCTGAGGAAGCACAACTCATCGCTACACAATTAGC
TAAAAAGGATCCTAAAAACGCTAAGGTTTATCAAAAAAATGCTGATCAATTTAGTGACAAGGCAATGGCTATTGCAGAGAAGTATAAGCCAAAATTT
AAAGCTGCAAAGTCTAAATACTTTGTGACTTCACATACAGCATTCTCATACTTAGCTAAGCGATACGGATTGACTCAGTTAGGTATTGCAGGTGTCT
CAACCGAGCAAGAACCTAGTGCTAAAAAATTAGCCGAAATTCAGGAGTTTGTGAAAACATATAAGGTTAAGACTATTTTTGTTGAAGAAGGAGTCTC
ACCTAAATTAGCTCAAGCAGTAGCTTCAGCTACTCGAGTTAAAATTGCAAGTTTAAGTCCTTTARAAGCAGTTCCCAAAAACAATAAAGATTACTTA
GAAAATTTGGAAACTAATCTTAAGGTACTTGTCAAATCGTTAAATCAATAG

SEQ ID NO. 40

MKRIRKSLIFVLGVVTLICLCACTKQSQQKNGLSVVTSFYPVYSITKAVSGDLNDIKMIRSQSGIHGFEPSSSDVAAIYDADLFLYHSHTLEAWARR
LEPSLHHSKVSVIEASKGMTLDKVHGLEDVEAEKGVDESTLYDPHTWNDPVKVSEEAQLIATQLAKKDPKNAKVYQKNADQFSDKAMAIAEKYKPKF
KAAKSKYFVTSHTAFSYLAKRYGLTQLGIAGVSTEQEPSAKKLAEIQEFVKTYKVKTIFVEEGVSPKLAQAVASATRVKIASLSPLXAVPKNNKDYL
ENLETNLKVLVKSLNQ

The nucleotide and amino acid sequences of GBS 85 in Ref. 3 are SEQ ID 215 and SEQ ID 216. These sequences are set forth below as SEQ ID NOS 41 and 42:

SEQ ID NO. 41

ATGCCTAAGAAGAAATCAGATACCCCAGAAAAAGAAGAAGTTGTCTTAACGGAATGGCAAAAGCGTAACCTTGAATTTTTAAAAAAACGCAAAGAAG
ATGAAGAAGAACAAAAACGTATTAACGAAAAATTACGCTTAGATAAAAGAAGTAAATTAAATATTTCTTCTCCTGAAGAACCTCAAAATACTACTAA
AATTAAGAAGCTTCATTTTCCAAAGATTTCAAGACCTAAGATTGAAAAGAAACAGAAAAAAGAAAAAATAGTCAACAGCTTAGCCAAAACTAATCGC
ATTAGAACTGCACCTATATTTGTAGTAGCATTCCTAGTCATTTTAGTTTCCGTTTTCCTACTAACTCCTTTTAGTAAGCAAAAAACAATAACAGTTA
GTGGAAATCAGCATACACCTGATGATATTTTGATAGAGAAAACGAATATTCAAAAAAACGATTATTTCTTTTCTTTAATTTTTAAACATAAAGCTAT
TGAACAACGTTTAGCTGCAGAAGATGTATGGGTAAAAACAGCTCAGATGACTTATCAATTTCCCAATAAGTTTCATATTCAAGTTCAAGAAAATAAG
ATTATTGCATATGCACATACAAAGCAAGGATATCAACCTGTCTTGGAAACTGGAAAAAAGGCTGATCCTGTAAATAGTTCAGAGCTACCAAAGCACT
TCTTAACAATTAACCTTGATAAGGAAGATAGTATTAAGCTATTAATTAAAGATTTAAAGGCTTTAGACCCTGATTTAATAAGTGAGATTCAGGTGAT
AAGTTTAGCTGATTCTAAAACGACACCTGACCTCCTGCTGTTAGATATGCACGATGGAAATAGTATTAGAATACCATTATCTAAATTTAAAGAAAGA
CTTCCTTTTTACAAACAAATTAAGAAGAACCTTAAGGAACCTTCTATTGTTGATATGGAAGTGGGAGTTTACACAACAACAAATACCATTGAATCAA
CCCCTGTTAAAGCAGAAGATACAAAAAATAAATCAACTGATAAAACACAAACACAAAATGGTCAGGTTGCGGAAAATAGTCAAGGACAAACAAATAA
CTCAAATACTAATCAACAAGGACAACAGATAGCAACAGAGCAGGCACCTAACCCTCAAAATGTTAAT

SEQ ID NO. 42

MPKKKSDTPEKEEVVLTEWQKRNLEFLKKRKEDEEEQKRINEKLRLDKRSKLNISSPEEPQNTTKIKKLHFPKISRPKIEKKQKKEKIVNSLAKTNR
IRTAPIFVVAFLVILVSVFLLTPFSKQKTITVSGNQHTPDDILIEKTNIQKNDYFFSLIFKHKAIEQRLAAEDVWVKTAQMTYQFPNKFHIQVQENK
IIAYAHTKQGYQPVLETGKKADPVNSSELPKHFLTINLDKEDSIKLLIKDLKALDPDLISEIQVISLADSKTTPDLLLLDMHDGNSIRIPLSKFKER
LPFYKQIKKNLKEPSIVDMEVGVYTTTNTIESTPVKAEDTKNKSTDKTQTQNGQVAENSQGQTNNSNTNQQGQQIATEQAPNPQNVN

GBS polypeptides of the invention may be present in the composition as individual separate polypeptides. It is preferred, however, that two or more (*i.e.* 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20) of the antigens are expressed as a single polypeptide chain (a 'hybrid' polypeptide). Hybrid polypeptides offer two principal advantages: first, a polypeptide that may be unstable or poorly expressed on its own can be assisted by adding a suitable hybrid partner that overcomes the problem; second, commercial manufacture is simplified as only one expression and purification need be employed in order to produce two polypeptides which are both antigenically useful.

The hybrid polypeptide may comprise two or more polypeptide sequences from the first antigen group. Accordingly, the invention includes a composition comprising a first amino acid sequence and a second amino acid sequence, wherein said first and second amino acid sequences are selected from a GBS antigen or a fragment thereof. Preferably, the first and second amino acid sequences in the hybrid polypeptide comprise different epitopes.

The hybrid polypeptide may comprise one or more polypeptide sequences from different GBS serotypes. Accordingly, the invention includes a composition comprising a first amino acid sequence and a second amino acid sequence, said first amino acid sequence and said second amino acid sequence selected from a GBS serotype selected from the group consisting of serotypes Ia, Ib, Ia/c, II, III, IV, V, VI, VII and VIII. The first and second amino acid sequence may be from the same GBS serotype or they may be from different GBS serotypes. Preferably, the first and second amino acid sequence are selected a GBS serotype selected from the group consisting of serotypes II and V. Most preferably, at least one of the first and second amino acid sequences is from GBS serotype V. Preferably, the first and second amino acid sequences in the hybrid polypeptide comprise difference epitopes.

In one embodiment, the hybrid polypeptide comprises one or more GBS antigens from serotype V. Preferably, the hybrid polypeptide comprises a first amino acid sequence and a second amino acid sequence, said first amino acid sequence and said second amino acid sequence comprising a GBS antigen or a fragment thereof selected from the group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691. Preferably, the GBS antigen or fragment thereof is selected from the group consisting of GBS 80 and GBS 691. Preferably, the first and second amino acid sequences in the hybrid polypeptide comprise difference epitopes.

Hybrids consisting of amino acid sequences from two, three, four, five, six, seven, eight, nine, or ten GBS antigens are preferred. In particular, hybrids consisting of amino acid sequences from two, three, four, or five GBS antigens are preferred.

Different hybrid polypeptides may be mixed together in a single formulation. Within such combinations, a GBS antigen may be present in more than one hybrid polypeptide and/or as a non-hybrid polypeptide. It is preferred, however, that an antigen is present either as a hybrid or as a non-hybrid, but not as both.

Preferably, the GBS antigen in one of the hybrid polypeptides is GBS 80 or a fragment thereof. Accordingly, examples of two-antigen hybrids for use in the invention may comprise: (1) GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313, (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 656, (16) GBS 80 and GBS 690, and (17) GBS 80 and GBS 691. Preferably, a two-antigen hybrid for use in the invention comprises GBS 80 and GBS 691.

Hybrid polypeptides can be represented by the formula **NH_2-A-{-X-L-}$_n$-B-COOH**, wherein: X is an amino acid sequence of a GBS antigen or a fragment thereof; L is an optional linker amino acid sequence; A is an optional N-terminal amino acid sequence; B is an optional C-terminal amino acid sequence; and *n* is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

If a -X- moiety has a leader peptide sequence in its wild-type form, this may be included or omitted in the hybrid protein. In some embodiments, the leader peptides will be deleted except for that of the -X- moiety located at the N-terminus of the hybrid protein *i.e.* the leader peptide of X_1 will be retained, but the leader peptides of X_2 ... X_n will be omitted. This is equivalent to deleting all leader peptides and using the leader peptide of X_1 as moiety -A-.

For each *n* instances of {-X-L-}, linker amino acid sequence -L- may be present or absent. For instance, when -*n*=2 the hybrid may be NH_2-X_1-L_1-X_2-L_2-COOH, NH_2-X_1-X_2-COOH, NH_2-X_1-L_1-X_2-COOH, NH_2-X_1-X_2-L_2-COOH, *etc.* Linker amino acid sequence(s) -L- will typically be short (*e.g.* 20 or fewer amino acids *i.e.* 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples comprise short peptide sequences which facilitate cloning, poly-glycine linkers (*i.e.* comprising Gly_n where n = 2, 3, 4, 5, 6, 7, 8, 9, 10 or more), and histidine tags (*i.e.* His_n where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable linker amino acid sequences will be apparent to those skilled in the art. A useful linker is GSGGGG (SEQ ID 1), with the Gly-Ser dipeptide being formed from a *Bam*HI restriction site, thus aiding cloning and manipulation, and the $(Gly)_4$ tetrapeptide being a typical poly-glycine linker.

-A- is an optional N-terminal amino acid sequence. This will typically be short (*e.g.* 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct protein trafficking, or short peptide sequences which facilitate cloning or purification (*e.g.* histidine tags *i.e.* His_n where $n = 3, 4, 5, 6, 7, 8, 9, 10$ or more). Other suitable N-terminal amino acid sequences will be apparent to those skilled in the art. If X_1 lacks its own N-terminus methionine, -A- is preferably an oligopeptide (*e.g.* with 1, 2, 3, 4, 5, 6, 7 or 8 amino acids) which provides a N-terminus methionine.

-B- is an optional C-terminal amino acid sequence. This will typically be short (*e.g.* 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include sequences to direct protein trafficking, short peptide sequences which facilitate cloning or purification (*e.g.* comprising histidine tags *i.e.* His_n where $n = 3, 4, 5, 6, 7, 8, 9, 10$ or more), or sequences which enhance protein stability. Other suitable C-terminal amino acid sequences will be apparent to those skilled in the art.

Most preferably, n is 2 or 3.

The saccharide antigen

The saccharide antigen is generally the capsular polysaccharide of a GBS or a derivative thereof. Suitable derivatives include oligosaccharide (*e.g.* from 3 to 150, preferably 8 to 100, monosaccharide units) fragments of the polysaccharide (*e.g.* refs. 12 to 16), de-acetylated saccharides (Ref. 16), N-acroylated saccharides (16), saccharides with terminal aldehyde groups, *etc.*

The saccharide is preferably conjugated to a carrier molecule to enhance immunogenicity (*e.g.* see refs. 4 to 23 *etc.*). In some embodiments of the invention the GBS saccharide is conjugated to a GBS protein as defined above, thereby giving a polypeptide/saccharide combination of the invention in a single molecule. In other embodiments the GBS saccharide is conjugated to a non-GBS protein, in which case the conjugate will be combined with a separate GBS protein to give a polypeptide/saccharide combination of the invention.

Non-GBS carrier polypeptides include tetanus toxoid, the *N.meningitidis* outer membrane protein (24), synthetic peptides (25, 26), heat shock proteins (27, 28), pertussis proteins (29, 30), protein D from *H.influenzae* (31), cytokines (32), lymphokines (32), hormones (32), growth factors (32), toxin A or B from *C.difficile* (33), iron-uptake proteins (34) *etc.* Preferred carrier proteins are the CRM197 diphtheria toxoid (35) and tetanus toxoid.

The saccharide and polypeptide are joined covalently. This may involve a direct covalent bond between the saccharide and polypeptide, or indirect coupling via a linker or spacer may be used (*e.g.* via a B-propionamido linker (16), *etc.*). Any suitable conjugation chemistry may be used (*e.g* reductive amination (21) *etc.*). Linkage is preferably via a terminal saccharide in the polysaccharide.

A single carrier molecule may carry saccharide antigens of a single type (*e.g.* saccharides derived from a single GBS serotype) or may carry multiple different antigens (*e.g.* saccharides derived from multiple GBS serotypes, all conjugated to the same carrier).

The saccharides can, of course, be prepared by various means (*e.g.* purification of the saccharide from GBS, chemical synthesis, *etc.*), in various sizes (*e.g.* full-length, fragmented, *etc.*) and may be derivatised for linking to carriers. They are preferably prepared in substantially pure form (*i.e.* substantially free from other streptococcal saccharides) or substantially isolated form. Processes for preparing capsular polysaccharides from GBS are well known in the art (*e.g.* refs. 36 to 39) and processes for preparing oligosaccharides from polysaccharides are also known (*e.g.* hydrolysis, sonication, enzymatic treatment, treatment with a base followed by nitrosation, *etc.* (12 to 16)).

As an alternative to using a saccharide antigen in non-conjugated combinations, a peptide mimetic of the GBS capsular polysaccharide may be used (*e.g.* 40). Suitable peptides can be selected by techniques such as phage display using protective anti-saccharide antibodies. As a further alternative, an anti-idiotypic antibody may be used instead of a saccharide antigen (*e.g.* ref. 41).

Prime/boost schedules

Polypeptide/saccharide combinations of the invention may be given as single doses or as part of a prime/boost schedule. In a prime/boost schedule, the combinations may be used as the priming dose, the boosting dose(s), or both.

If a combination is used for both priming and boosting, it is preferred to use the same combination both times. If a combination is used for only one of priming and boosting, it is preferred that the other dose should use the polypeptide or saccharide on which the combination is based. Thus the invention provides a prime-boost schedule where either (i) one of the saccharide and polypeptide antigens is used for priming an immune response and a combination are used for boosting the response, or (ii) combined saccharide and polypeptide antigens are used for priming an immune response but only one is used for boosting the response.

Various timings for priming and boosting are suitable for use with the invention. In one embodiment, a priming dose is given to a child and a booster is given to a teenager (13-18 years) or young adult (19-25 years). In another embodiment, a priming dose is given to a teenager or young adult and a booster is given during pregnancy. In another embodiment, a priming dose is given to a female who intends to become pregnant and a booster is given during pregnancy.

Immunogenic pharmaceutical compositions

Polypeptide/saccharide combinations are formulated as immunogenic compositions, and more preferably as compositions suitable for use as a vaccine in humans (*e.g.* children or adults).

Vaccines of the invention may either be prophylactic (*i.e.* to prevent infection) or therapeutic (*i.e.* to treat disease after infection), but will typically be prophylactic. Accordingly, the invention includes a method for the therapeutic or prophylactic treatment of GBS infection in an animal susceptible to GBS infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic compositions of the invention.

The composition of the invention is preferably sterile.

The composition of the invention is preferably pyrogen-free.

The composition of the invention generally has a pH of between 6.0 and 7.0, more preferably to between 6.3 and 6.9 *e.g.* 6.6$\pm$0.2. The composition is preferably buffered at this pH.

Other components suitable for human administration are disclosed in reference 42.

Vaccines of the invention may be administered in conjunction with other immunoregulatory agents. In particular, compositions will usually include an adjuvant. Preferred further adjuvants include, but are not limited to, one or more of the following set forth below:

A. Mineral Containing Compositions

Mineral containing compositions suitable for use as adjuvants in the invention include mineral salts, such as aluminium salts and calcium salts. The invention includes mineral salts such as hydroxides (*e.g.* oxyhydroxides), phosphates (*e.g.* hydroxyphoshpates, orthophosphates), sulphates, *etc.* {*e.g.* see chapters 8 & 9 of ref. 43}), or mixtures of different mineral compounds, with the compounds taking any suitable form (*e.g.* gel, crystalline, amorphous, *etc.*), and with adsorption being preferred. The mineral containing compositions may also be formulated as a particle of metal salt. See ref. 44.

B. Oil-Emulsions

Oil-emulsion compositions suitable for use as adjuvants in the invention include squalene-water emulsions, such as MF59 (5% Squalene, 0.5% Tween 80, and 0.5% Span 85, formulated into submicron particles using a microfluidizer). See ref. 45.

Complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA) may also be used as adjuvants in the invention.

C. Saponin Formulations

Saponin formulations, may also be used as adjuvants in the invention. Saponins are a heterologous group of sterol glycosides and triterpenoid glycosides that are found in the bark, leaves, stems, roots and even flowers of a wide range of plant species. Saponin from the bark of the *Quillaia saponaria* Molina tree have been widely studied as adjuvants. Saponin can also be commercially obtained from *Smilax ornata* (sarsaprilla), *Gypsophilla paniculata* (brides veil), and *Saponaria officianalis* (soap root). Saponin adjuvant formulations include purified formulations, such as QS21, as well as lipid formulations, such as ISCOMs.

Saponin compositions have been purified using High Performance Thin Layer Chromatography (HP-LC) and Reversed Phase High Performance Liquid Chromatography (RP-

HPLC). Specific purified fractions using these techniques have been identified, including QS7, QS17, QS18, QS21, QH-A, QH-B and QH-C. Preferably, the saponin is QS21. A method of production of QS21 is disclosed in U.S. Patent No. 5,057,540. Saponin formulations may also comprise a sterol, such as cholesterol (see WO 96/33739).

Combinations of saponins and cholesterols can be used to form unique particles called Immunostimulating Complexs (ISCOMs). ISCOMs typically also include a phospholipid such as phosphatidylethanolamine or phosphatidylcholine. Any known saponin can be used in ISCOMs. Preferably, the ISCOM includes one or more of Quil A, QHA and QHC. ISCOMs are further described in EP 0 109 942, WO 96/11711 and WO 96/33739. Optionally, the ISCOMS may be devoid of additional detergent. See ref. 46.

A review of the development of saponin based adjuvants can be found at ref. 47.

C. <u>Virosomes and Virus Like Particles (VLPs)</u>

Virosomes and Virus Like Particles (VLPs) can also be used as adjuvants in the invention. These structures generally contain one or more proteins from a virus optionally combined or formulated with a phospholipid. They are generally non-pathogenic, non-replicating and generally do not contain any of the native viral genome. The viral proteins may be recombinantly produced or isolated from whole viruses. These viral proteins suitable for use in virosomes or VLPs include proteins derived from influenza virus (such as HA or NA), Hepatitis B virus (such as core or capsid proteins), Hepatitis E virus, measles virus, Sindbis virus, Rotavirus, Foot-and-Mouth Disease virus, Retrovirus, Norwalk virus, human Papilloma virus, HIV, RNA-phages, Qß-phage (such as coat proteins), GA-phage, fr-phage, AP205 phage, and Ty (such as retrotransposon Ty protein p1). VLPs are discussed further in WO 03/024480, WO 03/024481, and Refs. 48, 49, 50 and 51. Virosomes are discussed further in, for example, Ref. 52

D. <u>Bacterial or Microbial Derivatives</u>

Adjuvants suitable for use in the invention include bacterial or microbial derivatives such as:

(1) *Non-toxic derivatives of enterobacterial lipopolysaccharide (LPS)*

Such derivatives include Monophosphoryl lipid A (MPL) and 3-O-deacylated MPL (3dMPL). 3dMPL is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains. A preferred "small particle" form of 3 De-O-acylated monophosphoryl lipid A is disclosed in EP 0 689 454. Such "small particles" of 3dMPL are small enough to be sterile filtered through a 0.22 micron membrane (see EP 0 689 454). Other non-toxic LPS derivatives include monophosphoryl lipid A mimics, such as aminoalkyl glucosaminide phosphate derivatives *e.g.* RC-529. See Ref. 53.

(2) *Lipid A Derivatives*

Lipid A derivatives include derivatives of lipid A from *Escherichia coli* such as OM-174. OM-174 is described for example in Ref. 54 and 55.

(3) *Immunostimulatory oligonucleotides*

Immunostimulatory oligonucleotides suitable for use as adjuvants in the invention include nucleotide sequences containing a CpG motif (a sequence containing an unmethylated cytosine followed by guanosine and linked by a phosphate bond). Bacterial double stranded RNA or oligonucleotides containing palindromic or poly(dG) sequences have also been shown to be immunostimulatory.

The CpG's can include nucleotide modifications/analogs such as phosphorothioate modifications and can be double-stranded or single-stranded. Optionally, the guanosine may be replaced with an analog such as 2'-deoxy-7-deazaguanosine. See ref. 56, WO 02/26757 and WO 99/62923 for examples of possible analog substitutions. The adjuvant effect of CpG oligonucleotides is further discussed in Refs. 57, 58, WO 98/40100, U.S. Patent No. 6,207,646, U.S. Patent No. 6,239,116, and U.S. Patent No. 6,429,199.

The CpG sequence may be directed to TLR9, such as the motif GTCGTT or TTCGTT. See ref. 59. The CpG sequence may be specific for inducing a Th1 immune response, such as a CpG-A ODN, or it may be more specific for inducing a B cell response, such a CpG-B ODN. CpG-A and CpG-B ODNs are discussed in refs. 60, 61 and WO 01/95935. Preferably, the CpG is a CpG-A ODN. Preferably, the CpG oligonucleotide is constructed so that the 5' end is accessible for receptor recognition. Optionally, two CpG oligonucleotide sequences may be attached at their 3' ends to form "immunomers". See, for example, refs. 62, 63, 64 and WO 03/035836.

(4) *ADP-ribosylating toxins and detoxified derivatives thereof.*

Bacterial ADP-ribosylating toxins and detoxified derivatives thereof may be used as adjuvants in the invention. Preferably, the protein is derived from *E. coli* (i.e., E. coli heat labile enterotoxin "LT), cholera ("CT"), or pertussis ("PT"). The use of detoxified ADP-ribosylating toxins as mucosal adjuvants is described in WO 95/17211 and as parenteral adjuvants in WO 98/42375. Preferably, the adjuvant is a detoxified LT mutant such as LT-K63, LT-R72, and LTR192G. The use of ADP-ribosylating toxins and detoxified derivaties thereof, particularly LT-K63 and LT-R72, as adjuvants can be found in Refs. 65, 66, 67, 68, 69, 70, 71 and 72 each of which is specifically incorporated by reference herein in their entirety. Numerical reference for amino acid substitutions is preferably based on the alignments of the A and B subunits of ADP-ribosylating toxins set forth in Domenighini et al., Mol. Microbiol (1995) 15(6):1165 – 1167, specifically incorporated herein by reference in its entirety.

E. Human Immunomodulators

Human immunomodulators suitable for use as adjuvants in the invention include cytokines, such as interleukins (*e.g.* IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12, *etc.*), interferons (*e.g.* interferon-γ), macrophage colony stimulating factor, and tumor necrosis factor.

F. Bioadhesives and Mucoadhesives

Bioadhesives and mucoadhesives may also be used as adjuvants in the invention. Suitable bioadhesives include esterified hyaluronic acid microspheres (Ref. 73) or mucoadhesives such as

cross-linked derivatives of poly(acrylic acid), polyvinyl alcohol, polyvinyl pyrollidone, polysaccharides and carboxymethylcellulose. Chitosan and derivatives thereof may also be used as adjuvants in the invention. E.g., ref. 74.

G. Microparticles

Microparticles may also be used as adjuvants in the invention. Microparticles (*i.e.* a particle of ~100nm to ~150μm in diameter, more preferably ~200nm to ~30μm in diameter, and most preferably ~500nm to ~10μm in diameter) formed from materials that are biodegradable and non-toxic (*e.g.* a poly(α-hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone, *etc.*), with poly(lactide-co-glycolide) are preferred, optionally treated to have a negatively-charged surface (*e.g.* with SDS) or a positively-charged surface (*e.g.* with a cationic detergent, such as CTAB).

H. Liposomes

Examples of liposome formulations suitable for use as adjuvants are described in U.S. Patent No. 6,090,406, U.S. Patent No. 5,916,588, and EP 0 626 169.

I. Polyoxyethylene ether and Polyoxyethylene Ester Formulations

Adjuvants suitable for use in the invention include polyoxyethylene ethers and polyoxyethylene esters. Ref. 75. Such formulations further include polyoxyethylene sorbitan ester surfactants in combination with an octoxynol (Ref. 76) as well as polyoxyethylene alkyl ethers or ester surfactants in combination with at least one additional non-ionic surfactant such as an octoxynol (Ref. 77).

Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether (laureth 9), polyoxyethylene-9-steoryl ether, polyoxytheylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether.

J. Polyphosphazene (PCPP)

PCPP formulations are described, for example, in Ref. 78 and 79.

K. Muramyl peptides

Examples of muramyl peptides suitable for use as adjuvants in the invention include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), and N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine MTP-PE).

L. Imidazoquinolone Compounds.

Examples of imidazoquinolone compounds suitable for use adjuvants in the invention include Imiquamod and its homologues, described further in Ref. 80 and 81.

The invention may also comprise combinations of aspects of one or more of the adjuvants identified above. For example, the following adjuvant compositions may be used in the invention:

(1) a saponin and an oil-in-water emulsion (ref. 82);

(2) a saponin (e.g.., QS21) + a non-toxic LPS derivative (e.g., 3dMPL) (see WO 94/00153);

(3) a saponin (e.g.., QS21) + a non-toxic LPS derivative (e.g., 3dMPL) + a cholesterol;

(4) a saponin (*e.g.* QS21) + 3dMPL + IL-12 (optionally + a sterol) (Ref. 83);

combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions (Ref. 84);

(5) SAF, containing 10% Squalane, 0.4% Tween 80, 5% pluronic-block polymer L121, and thr-MDP, either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion.

(6) Ribi™ adjuvant system (RAS), (Ribi Immunochem) containing 2% Squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox™); and

(7) one or more mineral salts (such as an aluminum salt) + a non-toxic derivative of LPS (such as 3dPML).

Aluminium salts and MF59 are preferred adjuvants for parenteral immunisation. Mutant bacterial toxins are preferred mucosal adjuvants.

The composition may include an antibiotic.

GBS polypeptide(s) and saccharide(s) in the compositions of the invention will be present in 'immunologically effective amounts' *i.e.* the administration of that amount to an individual, either in a single dose or as part of a series, is effective for treatment or prevention of disease. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individual to be treated (*e.g.* non-human primate, primate, *etc.*), the capacity of the individual's immune system to synthesise antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials.

Typically, the compositions of the invention are prepared as injectables. Direct delivery of the compositions will generally be parenteral (*e.g.* by injection, either subcutaneously, intraperitoneally, intravenously or intramuscularly or delivered to the interstitial space of a tissue) or mucosal (*e.g.* oral or intranasal [85,86]). The compositions can also be administered into a lesion. The invention provides a syringe containing a composition of the invention.

Once formulated, the compositions of the invention can be administered directly to the subject. The subjects to be treated can be animals; in particular, human subjects can be treated. The vaccines are particularly useful for vaccinating children and teenagers, and more particularly females.

As well as GBS polypeptides and saccahrides, the composition of the invention may comprise further antigens. For example, the composition may comprise one or more of the following further antigens:

- antigens from *Helicobacter pylori* such as CagA [87 to 90], VacA [91, 92], NAP [93, 94, 95], HopX [*e.g.* 96], HopY [*e.g.* 96] and/or urease.
- a saccharide antigen from *N.meningitidis* serogroup A, C, W135 and/or Y, such as the oligosaccharide disclosed in ref. 97 from serogroup C [see also ref. 98] or the oligosaccharides of ref. 99.
- a saccharide antigen from *Streptococcus pneumoniae* [*e.g.* 100, 101, 102].
- an antigen from hepatitis A virus, such as inactivated virus [*e.g.* 103, 104].
- an antigen from hepatitis B virus, such as the surface and/or core antigens [*e.g.* 104, 105].
- an antigen from *Bordetella pertussis*, such as pertussis holotoxin (PT) and filamentous haemagglutinin (FHA) from *B.pertussis*, optionally also in combination with pertactin and/or agglutinogens 2 and 3 [*e.g.* refs. 106 & 107].
- a diphtheria antigen, such as a diphtheria toxoid [*e.g.* chapter 3 of ref. 108] *e.g.* the CRM_{197} mutant [*e.g.* 109].
- a tetanus antigen, such as a tetanus toxoid [*e.g.* chapter 4 of ref. 128].
- a saccharide antigen from *Haemophilus influenzae* B [*e.g.* 98].
- an antigen from hepatitis C virus [*e.g.* 110].
- an antigen from *N.gonorrhoeae* [*e.g.* 111, 112, 113, 114].
- an antigen from *Chlamydia pneumoniae* [*e.g.* refs. 115 to 121].
- an antigen from *Chlamydia trachomatis* [*e.g.* 122].
- an antigen from *Porphyromonas gingivalis* [*e.g.* 123].
- polio antigen(s) [*e.g.* 124, 125] such as OPV or, preferably, IPV.
- rabies antigen(s) [*e.g.* 126] such as lyophilised inactivated virus [*e.g.* 127, RabAvert™].
- measles, mumps and/or rubella antigens [*e.g.* chapters 9, 10 & 11 of ref. 128].
- influenza antigen(s) [*e.g.* chapter 19 of ref. 128], such as the haemagglutinin and/or neuraminidase surface proteins.
- an antigen from *Moraxella catarrhalis* [*e.g.* 129].
- an antigen from *Streptococcus pyogenes* (group A streptococcus) [*e.g.* 3, 130, 131].
- an antigen from *Staphylococcus aureus* [*e.g.* 132].
- an antigen from *Bacillus anthracis* [*e.g.* 133, 134, 135].
- an antigen from a virus in the flaviviridae family (genus flavivirus), such as from yellow fever virus, Japanese encephalitis virus, four serotypes of Dengue viruses, tick-borne encephalitis virus, West Nile virus.

- a pestivirus antigen, such as from classical porcine fever virus, bovine viral diarrhoea virus, and/or border disease virus.
- a parvovirus antigen *e.g.* from parvovirus B19.
- a prion protein (*e.g.* the CJD prion protein)
- an amyloid protein, such as a beta peptide [136]
- a cancer antigen, such as those listed in Table 1 of ref. 137 or in tables 3 & 4 of ref. 138.

The composition may comprise one or more of these further antigens.

Toxic protein antigens may be detoxified where necessary (*e.g.* detoxification of pertussis toxin by chemical and/or genetic means [107]).

Where a diphtheria antigen is included in the composition it is preferred also to include tetanus antigen and pertussis antigens. Similarly, where a tetanus antigen is included it is preferred also to include diphtheria and pertussis antigens. Similarly, where a pertussis antigen is included it is preferred also to include diphtheria and tetanus antigens. DTP combinations are thus preferred. Saccharide antigens are preferably in the form of conjugates. Carrier proteins for the conjugates are the same as those described above for GBS saccharide conjugation, with CRM197 being preferred.

Antigens in the composition will typically be present at a concentration of at least 1μg/ml each. In general, the concentration of any given antigen will be sufficient to elicit an immune response against that antigen.

As an alternative to using protein antigens in the composition of the invention, nucleic acid encoding the antigen may be used. Protein components of the compositions of the invention may thus be replaced by nucleic acid (preferably DNA *e.g.* in the form of a plasmid) that encodes the protein.

Methods of treating patients

The invention provides polypeptide/saccharide combinations of the invention for use as medicaments. The medicament is preferably able to raise an immune response in a mammal (*i.e.* it is an immunogenic composition) and is more preferably a vaccine.

The invention also provides a method of raising an immune response in a patient, comprising administering to a patient a composition of the invention. The immune response is preferably protective against streptococcal disease, and may comprise a humoral immune response and/or a cellular immune response.

The invention also provides the use of polypeptide/saccharide combination of the invention in the manufacture of a medicament for raising an immune response in an patient. The medicament is preferably an immunogenic composition (*e.g.* a vaccine). The medicament is preferably for the prevention and/or treatment of a disease caused by GBS (*e.g.* meningitis, sepsis, chorioamnionitis).

The invention also provides for a kit comprising a first component comprising the immunogenic compositions of the invention. The kit may further include a second component comprising one or more of the following: instructions, syringe or other delivery device, adjuvant, or pharmaceutically acceptable formulating solution.

The invention also provides a delivery device pre-filled with the immunogenic compositions of the invention.

The invention also provides a method for raising an immune response in a mammal comprising the step of administering an effective amount of a composition of the invention. The immune response is preferably protective and preferably involves antibodies and/or cell-mediated immunity. The method may raise a booster response.

Process for manufacturing

The invention provides a process for preparing a composition of the invention, comprising the step of mixing (i) one or more GBS polypeptide antigens with (ii) one or more GBS saccharide antigens.

The process may comprise the step of covalently linking the GBS polypeptide to the GBS saccharide in order to form a conjugate.

Definitions

The term "comprising" means "including" as well as "consisting" *e.g.* a composition "comprising" X may consist exclusively of X or may include something additional *e.g.* X + Y.

The term "about" in relation to a numerical value x means, for example, $x \pm 10\%$.

The word "substantially" does not exclude "completely" *e.g.* a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

MODES FOR CARRYING OUT THE INVENTION

GBS serotype III is grown in Todd-Hewitt broth as described in reference 36 and its capsular polysaccharide was purified. The polysaccharide is depolymerised, sized and purified as described in reference 14 to give oligosaccharide antigen. Similar procedures are used to prepare capsular polysaccharides from other GBS serotypes.

The oligosaccharide is either admixed with or covalently conjugated (directly or via a linker) to purified serotype V protein. Preferably, the protein comprises a GBS antigen or a fragment thereof selected from the group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention. All documents cited herein are incorporated by reference in their entirety.

REFERENCES (the contents of which are hereby incorporated by reference)

[1] Schuchat (1999) *Lancet* 353(9146):51-6.

[2] Tettelin *et al.* (2002) *Proc. Natl. Acad. Sci. USA*, 10.1073/pnas.182380799.

[3] International patent application WO02/34771.

[4] Kasper (1995) *Proc Assoc Am Physicians* 107:369-373.

[5] US patent 6,426,074.

[6] European patent application EP-A-0866133.

[7] US patent 5,820,860.

[8] US patent 5,648,241.

[9] US patent 5,834,444.

[10] International patent application WO91/04049.

[11] International patent application WO94/10317.

[12] International patent application WO87/06267.

[13] International patent application WO91/04335.

[14] US patent 6,372,222.

[15] International patent application WO96/40795.

[16] WO00/10599.

[17] US patent 5,302,386.

[18] International patent application WO94/06467.

[19] US patent 5,993,825.

[20] US patent 5,843,461.

[21] US patent 5,795,580.

[22] International patent application WO98/09648.

[23] US patent 6,280,738.

[24] EP-A-0372501

[25] EP-A-0378881

[26] EP-A-0427347

[27] WO93/17712

[28] WO94/03208

[29] WO98/58668

[30] EP-A-0471177

[31] WO00/56360

[32] WO91/01146

[33] WO00/61761

[34] WO01/72337

[35] *Research Disclosure*, 453077 (Jan 2002)

[36] US patent 4,207,414.

[37] US patent 4,324,887.

[38] US patent 4,367,221.

[39] US patent 4,367,223.

[40] Pincus *et al.* (1998) *J. Immunology* 160:293-298.

[41] International patent application WO99/54457.

[42] Gennaro (2000) *Remington: The Science and Practice of Pharmacy.* 20th edition, ISBN: 0683306472.

43. *Vaccine design:the subunit and adjuvant approach* (1995) Powell & Newman. ISBN 0-306-44867-X.

44. WO00/23105.

45. WO90/14837.

46. WO00/07621.

47. Barr, et al., "ISCOMs and other saponin based adjuvants", Advanced Drug Delivery Reviews (1998) 32:247 – 271. See also Sjolander, et al., "Uptake and adjuvant activity of orally delivered saponin and ISCOM vaccines", Advanced Drug Delivery Reviews (1998) 32:321 – 338.

48. Niikura et al., "Chimeric Recombinant Hepatitis E Virus-Like Particles as an Oral Vaccine Vehicle Presenting Foreign Epitopes", Virology (2002) 293:273 – 280.

49. Lenz et al., "Papillomarivurs-Like Particles Induce Acute Activation of Dendritic Cells", Journal of Immunology (2001) 5246 – 5355.

50. Pinto, et al., "Cellular Immune Responses to Human Papillomavirus (HPV)-16 L1 Healthy Volunteers Immunized with Recombinant HPV-16 L1 Virus-Like Particles", Journal of Infectious Diseases (2003) 188:327 – 338.

51. Gerber et al., "Human Papillomavrisu Virus-Like Particles Are Efficient Oral Immunogens when Coadministered with Escherichia coli Heat-Labile Entertoxin Mutant R192G or CpG", Journal of Virology (2001) 75(10):4752 – 4760.

52. Gluck et al., "New Technology Platforms in the Development of Vaccines for the Future", Vaccine (2002) 20:B10 –B16.

53. Johnson *et al.* (1999) *Bioorg Med Chem Lett* 9:2273-2278.

54. Meraldi et al., "OM-174, a New Adjuvant with a Potential for Human Use, Induces a Protective Response with Administered with the Synthetic C-Terminal Fragment 242-310 from the circumsporozoite protein of Plasmodium berghei", Vaccine (2003) 21:2485 – 2491.

55. Pajak, et al., "The Adjuvant OM-174 induces both the migration and maturation of murine dendritic cells in vivo", Vaccine (2003) 21:836 – 842.

56. Kandimalla, et al., "Divergent synthetic nucleotide motif recognition pattern: design and development of potent immunomodulatory oligodeoxyribonucleotide agents with distinct cytokine induction profiles", Nucleic Acids Research (2003) 31(9): 2393 – 2400.

57. Krieg, "CpG motifs: the active ingredient in bacterial extracts?", Nature Medicine (2003) 9(7): 831 – 835.

58. McCluskie, et al., "Parenteral and mucosal prime-boost immunization strategies in mice with hepatitis B surface antigen and CpG DNA", FEMS Immunology and Medical Microbiology (2002) 32:179 – 185.

59. Kandimalla, et al., "Toll-like receptor 9: modulation of recognition and cytokine induction by novel synthetic CpG DNAs", Biochemical Society Transactions (2003) 31 (part 3): 654 – 658.

60. Blackwell, et al., "CpG-A-Induced Monocyte IFN-gamma-Inducible Protein-10 Production is Regulated by Plasmacytoid Dendritic Cell Derived IFN-alpha", J. Immunol. (2003) 170(8):4061 – 4068.

61. Krieg, "From A to Z on CpG", TRENDS in Immunology (2002) 23(2): 64 – 65.

62. Kandimalla, et al., "Secondary structures in CpG oligonucleotides affect immunostimulatory activity", BBRC (2003) 306:948 – 953.

63. Kandimalla, et al., "Toll-like receptor 9: modulation of recognition and cytokine induction by novel synthetic GpG DNAs", Biochemical Society Transactions (2003) 31(part 3):664 – 658.

64. Bhagat et al., "CpG penta- and hexadeoxyribonucleotides as potent immunomodulatory agents" BBRC (2003) 300:853 – 861.

65 Beignon, et al., "The LTR72 Mutant of Heat-Labile Enterotoxin of Escherichia coli Enahnces the Ability of Peptide Antigens to Elicit CD4+ T Cells and Secrete Gamma Interferon after Coapplication onto Bare Skin", Infection and Immunity (2002) 70(6):3012 – 3019.

66 Pizza, et al., "Mucosal vaccines: non toxic derivatives of LT and CT as mucosal adjuvants", Vaccine (2001) 19:2534 – 2541.

67 Pizza, et al., "LTK63 and LTR72, two mucosal adjuvants ready for clinical trials" Int. J. Med. Microbiol (2000) 290(4-5):455-461.

68 Scharton-Kersten et al., "Transcutaneous Immunization with Bacterial ADP-Ribosylating Exotoxins, Subunits and Unrelated Adjuvants", Infection and Immunity (2000) 68(9):5306 – 5313.

69 Ryan et al., "Mutants of Escherichia coli Heat-Labile Toxin Act as Effective Mucosal Adjuvants for Nasal Delivery of an Acellular Pertussis Vaccine: Differential Effects of the Nontoxic AB Complex and Enzyme Activity on Th1 and Th2 Cells" Infection and Immunity (1999) 67(12):6270 – 6280.

70 Partidos et al., "Heat-labile enterotoxin of Escherichia coli and its site-directed mutant LTK63 enhance the proliferative and cytotoxic T-cell responses to intranasally co-immunized synthetic peptides", Immunol. Lett. (1999) 67(3):209 – 216.

71 Peppoloni et al., "Mutants of the Escherichia coli heat-labile enterotoxin as safe and strong adjuvants for intranasal delivery of vaccines", Vaccines (2003) 2(2):285 – 293.

72 Pine et al., (2002) "Intranasal immunization with influenza vaccine and a detoxified mutant of heat labile enterotoxin from Escherichia coli (LTK63)" J. Control Release (2002) 85(1-3):263 – 270.

73. Singh *et al.* (2001) *J. Cont. Rele.* 70:267-276.

74. WO99/27960.

75. WO99/52549.

76. WO01/21207.

77. WO01/21152.

78. Andrianov et al., "Preparation of hydrogel microspheres by coacervation of aqueous polyphophazene solutions", Biomaterials (1998) 19(1 – 3):109 – 115.

79. Payne et al., "Protein Release from Polyphosphazene Matrices", Adv. Drug. Delivery Review (1998) 31(3):185 – 196.

80. Stanley, "Imiquimod and the imidazoquinolones: mechanism of action and therapeutic potential" Clin Exp Dermatol (2002) 27(7):571 – 577.

81. Jones, "Resiquimod 3M", Curr Opin Investig Drugs (2003) 4(2):214 – 218.

82. WO99/11241.

83. WO98/57659.

84. European patent applications 0835318, 0735898 and 0761231.

[85] Bakke *et al.* (2001) *Infect. Immun.* 69:5010-5015.

[86] Katial *et al.* (2002) *Infect. Immun.* 70:702-707.

[87] Covacci & Rappuoli (2000) *J. Exp. Med.* 19:587-592.

[88] WO93/18150.

[89] Covacci *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90: 5791-5795.

[90] Tummuru *et al.* (1994) *Infect. Immun.* 61:1799-1809.

[91] Marchetti *et al.* (1998) *Vaccine* 16:33-37.

[92] Telford *et al.* (1994) *J. Exp. Med.* 179:1653-1658.

[93] Evans *et al.* (1995) *Gene* 153:123-127.
[94] WO96/01272 & WO96/01273, especially SEQ ID NO:6.
[95] WO97/25429.
[96] WO98/04702.
[97] Costantino *et al.* (1992) *Vaccine* 10:691-698.
[98] Costantino *et al.* (1999) *Vaccine* 17:1251-1263.
[99] International patent application PCT/IB02/03191.
[100] Watson (2000) *Pediatr Infect Dis J* 19:331-332.
[101] Rubin (2000) *Pediatr Clin North Am* 47:269-285, v.
[102] Jedrzejas (2001) *Microbiol Mol Biol Rev* 65:187-207.
[103] Bell (2000) *Pediatr Infect Dis J* 19:1187-1188.
[104] Iwarson (1995) *APMIS* 103:321-326.
[105] Gerlich *et al.* (1990) *Vaccine* 8 Suppl:S63-68 & 79-80.
[106] Gustafsson *et al.* (1996) *N. Engl. J. Med.* 334:349-355.
[107] Rappuoli *et al.* (1991) *TIBTECH* 9:232-238.
[108] *Vaccines* (1988) eds. Plotkin & Mortimer. ISBN 0-7216-1946-0.
[109] Del Guidice *et al.* (1998) *Molecular Aspects of Medicine* 19:1-70.
[110] Hsu *et al.* (1999) *Clin Liver Dis* 3:901-915.
[111] International patent application WO99/24578.
[112] International patent application WO99/36544.
[113] International patent application WO99/57280.
[114] International patent application PCT/IB02/02069.
[115] International patent application WO02/02606.
[116] Kalman *et al.* (1999) *Nature Genetics* 21:385-389.
[117] Read *et al.* (2000) *Nucleic Acids Res* 28:1397-406.
[118] Shirai *et al.* (2000) *J. Infect. Dis.* 181(Suppl 3):S524-S527.
[119] International patent application WO99/27105.
[120] International patent application WO00/27994.
[121] International patent application WO00/37494.
[122] International patent application WO99/28475.
[123] Ross *et al.* (2001) *Vaccine* 19:4135-4142.
[124] Sutter *et al.* (2000) *Pediatr Clin North Am* 47:287-308.
[125] Zimmerman & Spann (1999) *Am Fam Physician* 59:113-118, 125-126.
[126] Dreesen (1997) *Vaccine* 15 Suppl:S2-6.
[127] *MMWR Morb Mortal Wkly Rep* 1998 Jan 16;47(1):12, 19.
[128] *Vaccines* (1988) eds. Plotkin & Mortimer. ISBN 0-7216-1946-0.
[129] McMichael (2000) *Vaccine* 19 Suppl 1:S101-107.
[130] Dale (1999) *Infect Dis Clin North Am* 13:227-43, viii.
[131] Ferretti *et al.* (2001) *PNAS USA* 98: 4658-4663.
[132] Kuroda *et al.* (2001) *Lancet* 357(9264):1225-1240; see also pages 1218-1219.
[133] *J Toxicol Clin Toxicol* (2001) 39:85-100.
[134] Demicheli *et al.* (1998) *Vaccine* 16:880-884.

[135] Stepanov *et al.* (1996) *J Biotechnol* 44:155-160.
[136] Ingram (2001) *Trends Neurosci* 24:305-307.
[137] Rosenberg (2001) *Nature* 411:380-384.
[138] Moingeon (2001) *Vaccine* 19:1305-1326.

CLAIMS:

1. An immunogenic composition comprising a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

2. The immunogenic composition of claim 1, wherein said GBS polypeptide antigens further comprise a GBS polypeptide or a fragment thereof of serogroup II.

3. The immunogenic composition of claim 1, wherein said GBS polypeptide antigen combination comprises GBS 80 or a fragment thereof.

4. The immunogenic composition of claim 3, wherein said GBS polypeptide antigens comprise a combination of two GBS antigens or fragments thereof selected from the group consisting of (1) GBS 80 and GBS 91, (2) GBS 80 and GBS 104, (3) GBS 80 and GBS 147, (4) GBS 80 and GBS 173, (5) GBS 80 and GBS 276, (6) GBS 80 and GBS 305, (7) GBS 80 and GBS 313, (8) GBS 80 and GBS 322, (9) GBS 80 and GBS 328, (10) GBS 80 and GBS 330, (11) GBS 80 and GBS 338, (12) GBS 80 and GBS 358, (13) GBS 80 and GBS 361, (14) GBS 80 and GBS 404, (14) GBS 80 and GBS 404, (15) GBS 80 and GBS 656, (16) GBS 80 and GBS 690, and (17) GBS 80 and GBS 691.

5. The immunogenic composition of claim 4, wherein said combination is selected from the group consisting of (1) GBS 80 and GBS 338; (2) GBS 80 and GBS 361, (3) GBS 80 and GBS 305, (4) GBS 80 and GBS 328, (5) GBS 80 and GBS 690, (6) GBS 80 and GBS 691 and (7) GBS 80 and GBS 147.

6. The immunogenic composition of claim 4, wherein said combination comprises GBS 80 and GBS 691.

7. The immunogenic composition of claim 1, wherein said composition comprises a combination of at least three GBS polypeptide antigens.

8. The immunogenic composition of claim 7, wherein said combination comprises GBS 80 and GBS 691.

9. The immunogenic composition of claim 7, wherein said combination comprises GBS 80.

10. The immunogenic composition of claim 1, wherein at least one GBS polypeptide antigen is covalently linked to the GBS saccharide antigen.

11. The immunogenic composition of claim 1, wherein said GBS saccharide antigen is covalently linked to a carrier protein.

12. The immunogenic composition of claim 11, wherein said carrier protein is selected from the group consisting of tetanus toxoid, diphtheria toxoid, *N. meningitides* outer membrane protein, heat shock protein, pertusis protein, protein D from *H. influenzae*, and toxin A or B from *C. difficile*.

13. The immunogenic composition of claim 12, wherein said carrier protein is selected from the group consisting of tetanus toxoid and diphtheria toxoid.

14. The immunogenic composition of claim 13, wherein said carrier protein is a diphtheria toxoid.

15. The immunogenic composition of claim 14, wherein said diphtheria toxoid is CRM197.

16. A method for the therapeutic or prophylactic treatment of GBS infection in an animal susceptible to GBS infection comprising administering to said animal a therapeutic or prophylactic amount of the immunogenic composition of claim 1.

17. A method for the manufacture of a medicament for raising an immune response against GBS comprising combining a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected from GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

SEQUENCE LISTING

SEQ ID NO. 1

ATGAAATTATCGAAGAAGTTATTGTTTTCGGCTGCTGTTTTAACAATGGTGGCGGGGTCAACTGTTGAACCAGTAGCTCAGTTTGC
GACTGGAATGAGTATTGTAAGAGCTGCAGAAGTGTCACAAGAACGCCCAGCGAAAACAACAGTAAATATCTATAAATTACAAGCTG
ATAGTTATAAATCGGAAATTACTTCTAATGGTGGTATCGAGAATAAAGACGGCGAAGTAATATCTAACTATGCTAAACTTGGTGAC
AATGTAAAAGGTTTGCAAGGTGTACAGTTTAAACGTTATAAAGTCAAGACGGATATTTCTGTTGATGAATTGAAAAAATTGACAAC
AGTTGAAGCAGCAGATGCAAAAGTTGGAACGATTCTTGAAGAAGGTGTCAGTCTACCTCAAAAAACTAATGCTCAAGGTTTGGTCG
TCGATGCTCTGGATTCAAAAAGTAATGTGAGATACTTGTATGTAGAAGATTTAAAGAATTCACCTTCAAACATTACCAAAGCTTAT
GCTGTACCGTTTGTGTTGGAATTACCAGTTGCTAACTCTACAGGTACAGGTTTCCTTTCTGAAATTAATATTTACCCTAAAAACGT
TGTAACTGATGAACCAAAAACAGATAAAGATGTTAAAAAATTAGGTCAGGACGATGCAGGTTATACGATTGGTGAAGAATTCAAAT
GGTTCTTGAAATCTACAATCCCTGCCAATTTAGGTGACTATGAAAAATTTGAAATTACTGATAAATTTGCAGATGGCTTGACTTAT
AAATCTGTTGGAAAAATCAAGATTGGTTCGAAAACACTGAATAGAGATGAGCACTACACTATTGATGAACCAACAGTTGATAACCA
AAATACATTAAAAATTACGTTTAAACCAGAGAAATTTAAAGAAATTGCTGAGCTACTTAAAGGAATGACCCTTGTTAAAAATCAAG
ATGCTCTTGATAAAGCTACTGCAAATACAGATGATGCGGCATTTTTGGAAATTCCAGTTGCATCAACTATTAATGAAAAAGCAGTT
TTAGGAAAAGCAATTGAAAATACTTTTGAACTTCAATATGACCATACTCCTGATAAAGCTGACAATCCAAAACCATCTAATCCTCC
AAGAAAACCAGAAGTTCATACTGGTGGAAACGATTTGTAAAGAAAGACTCAACAGAAACACAAACACTAGGTGGTGCTGAGTTTG
ATTTGTTGGCTTCTGATGGGACAGCAGTAAAATGGACAGATGCTCTTATTAAAGCGAATACTAATAAAAACTATATTGCTGGAGAA
GCTGTTACTGGGCAACCAATCAAATTGAAATCACATACAGACGGTACGTTTGAGATTAAAGGTTTGGCTTATGCAGTTGATGCGAA
TGCAGAGGGTACAGCAGTAACTTACAAATTAAAAGAAACAAAAGCACCAGAAGGTTATGTAATCCCTGATAAAGAAATCGAGTTTA
CAGTATCACAAACATCTTATAATACAAAACCAACTGACATCACGGTTGATAGTGCTGATGCAACACCTGATACAATTAAAAACAAC
AAACGTCCTTCAATCCCTAATACTGGTGGTATTGGTACGGCTATCTTTGTCGCTATCGGTGCTGCGGTGATGGCTTTTGCTGTTAA
GGGGATGAAGCGTCGTACAAAAGATAAC

SEQ ID NO: 2

MKLSKKLLFSAAVLTMVAGSTVEPVAQFATGMSIVRAAEVSQERPAKTTVNIYKLQADSYKSEITSNGGIENKDGEVISNYAKLGD
NVKGLQGVQFKRYKVKTDISVDELKKLTTVEAADAKVGTILEEGVSLPQKTNAQGLVVDALDSKSNVRYLYVEDLKNSPSNITKAY
AVPFVLELPVANSTGTGFLSEINIYPKNVVTDEPKTDKDVKKLGQDDAGYTIGEEFKWFLKSTIPANLGDYEKFEITDKFADGLTY
KSVGKIKIGSKTLNRDEHYTIDEPTVDNQNTLKITFKPEKFKEIAELLKGMTLVKNQDALDKATANTDDAAFLEIPVASTINEKAV
LGKAIENTFELQYDHTPDKADNPKPSNPPRKPEVHTGGKRFVKKDSTETQTLGGAEFDLLASDGTAVKWTDALIKANTNKNYIAGE
AVTGQPIKLKSHTDGTFEIKGLAYAVDANAEGTAVTYKLKETKAPEGYVIPDKEIEFTVSQTSYNTKPTDITVDSADATPDTIKNN
KRPSIPNTGGIGTAIFVAIGAAVMAFAVKGMKRRTKDN

SEQ ID NO. 3

ATGAAAAAAGGACAAGTAAATGATACTAAGCAATCTTACTCTCTACGTAAATATAAATTTGGTTTAGCATCAGTAATTTTAGGGTC
ATTCATAATGGTCACAAGTCCTGTTTTTGCGGATCAAACTACATCGGTTCAAGTTAATAATCAGACAGGCACTAGTGTGGATGCTA
ATAATTCTTCCAATGAGACAAGTGCGTCAAGTGTGATTACTTCCAATAATGATAGTGTTCAAGCGTCTGATAAAGTTGTAAATAGT
CAAAATACGGCAACAAAGGACATTACTACTCCTTTAGTAGAGACAAAGCCAATGGTGGAAAAAACATTACCTGAACAAGGGAATTA
TGTTTATAGCAAAGAAACCGAGGTGAAAAATACACCTTCAAAATCAGCCCCAGTAGCTTTCTATGCAAAGAAAGGTGATAAAGTTT
TCTATGACCAAGTATTTAATAAAGATAATGTGAAATGGATTTCATATAAGTCTTTTTGTGGCGTACGTCGATACGCAGCTATTGAG
TCACTAGATCCATCAGGAGGTTCAGAGACTAAAGCACCTACTCCTGTAACAAATTCAGGAAGCAATAATCAAGAGAAAATAGCAAC
GCAAGGAAATTATACATTTTCACATAAAGTAGAAGTAAAAAATGAAGCTAAGGTAGCGAGTCCAACTCAATTTACATTGGACAAAG
GAGACAGAATTTTTTACGACCAAATACTAACTATTGAAGGAAATCAGTGGTTATCTTATAAATCATTCAATGGTGTTCGTCGTTTT
GTTTTGCTAGGTAAAGCATCTTCAGTAGAAAAAACTGAAGATAAAGAAAAAGTGTCTCCTCAACCACAAGCCCGTATTACTAAAAC
TGGTAGACTGACTATTTCTAACGAAACAACTACAGGTTTTGATATTTTAATTACGAATATTAAAGATGATAACGGTATCGCTGCTG
TTAAGGTACCGGTTTGGACTGAACAAGGAGGGCAAGATGATATTAAATGGTATACAGCTGTAACTACTGGGGATGGCAACTACAAA
GTAGCTGTATCATTTGCTGACCATAAGAATGAGAAGGGTCTTTATAATATTCATTTATACTACCAAGAAGCTAGTGGGACACTTGT
AGGTGTAACAGGAACTAAAGTGACAGTAGCTGGAACTAATTCTTCTCAAGAACCTATTGAAAATGGTTTAGCAAAGACTGGTGTTT
ATAATATTATCGGAAGTACTGAAGTAAAAAATGAAGCTAAAATATCAAGTCAGACCCAATTTACTTTAGAAAAAGGTGACAAAATA
AATTATGATCAAGTATTGACAGCAGATGGTTACCAGTGGATTTCTTACAAATCTTATAGTGGTGTTCGTCGCTATATTCCTGTGAA
AAAGCTAACTACAAGTAGTGAAAAAGCGAAAGATGAGGCGACTAAACCGACTAGTTATCCCAACTTACCTAAAACAGGTACCTATA
CATTTACTAAAACTGTAGATGTGAAAAGTCAACCTAAAGTATCAAGTCCAGTGGAATTTAATTTTCAAAAGGGTGAAAAAAATACAT
TATGATCAAGTGTTAGTAGTAGATGGTCATCAGTGGATTTCATACAAGAGTTATTCCGGTATTCGTCGCTATATTGAAATT

SEQ ID NO. 4

MKKGQVNDTKQSYSLRKYKFGLASVILGSFIMVTSPVFADQTTSVQVNNQTGTSVDANNSSNETSASSVITSNNDSVQASDKVVNS
QNTATKDITTPLVETKPMVEKTLPEQGNYVYSKETEVKNTPSKSAPVAFYAKKGDKVFYDQVFNKDNVKWISYKSFCGVRRYAAIE
SLDPSGGSETKAPTPVTNSGSNNQEKIATQGNYTFSHKVEVKNEAKVASPTQFTLDKGDRIFYDQILTIEGNQWLSYKSFNGVRRF
VLLGKASSVEKTEDKEKVSPQPQARITKTGRLTISNETTTGFDILITNIKDDNGIAAVKVPVWTEQGGQDDIKWYTAVTTGDGNYK
VAVSFADHKNEKGLYNIHLYYQEASGTLVGVTGTKVTVAGTNSSQEPIENGLAKTGVYNIIGSTEVKNEAKISSQTQFTLEKGDKI

NYDQVLTADGYQWISYKSYSGVRRYIPVKKLTTSSEKAKDEATKPTSYPNLPKTGTYTFTKTVDVKSQPKVSSPVEFNFQKGEKIH
YDQVLVVDGHQWISYKSYSGIRRYIEI

SEQ ID NO. 5

ATGAAAAAGAGACAAAAAATATGGAGAGGGTTATCAGTTACTTTACTAATCCTGTCCCAAATTCCATTTGGTATATTGGTACAAGG
TGAAACCCAAGATACCAATCAAGCACTTGGAAAAGTAATTGTTAAAAAAACGGGAGACAATGCTACACCATTAGGCAAAGCGACTT
TTGTGTTAAAAAATGACAATGATAAGTCAGAAACAAGTCACGAAACGGTAGAGGGTTCTGGAGAAGCAACCTTTGAAAACATAAAA
CCTGGAGACTACACATTAAGAGAAGAAACAGCACCAATTGGTTATAAAAAAACTGATAAAACCTGGAAAGTTAAAGTTGCAGATAA
CGGAGCAACAATAATCGAGGGTATGGATGCAGATAAAGCAGAGAAACGAAAAGAAGTTTTGAATGCCCAATATCCAAAATCAGCTA
TTTATGAGGATACAAAAGAAAATTACCCATTAGTTAATGTAGAGGGTTCCAAAGTTGGTGAACAATACAAAGCATTGAATCCAATA
AATGGAAAAGATGGTCGAAGAGAGATTGCTGAAGGTTGGTTATCAAAAAAAATTACAGGGGTCAATGATCTCGATAAGAATAAATA
TAAAATTGAATTAACTGTTGAGGGTAAAACCACTGTTGAAACGAAAGAACTTAATCAACCACTAGATGTCGTTGTGCTATTAGATA
ATTCAAATAGTATGAATAATGAAAGAGCCAATAATTCTCAAAGAGCATTAAAAGCTGGGGAAGCAGTTGAAAAGCTGATTGATAAA
ATTACATCAAATAAAGACAATAGAGTAGCTCTTGTGACATATGCCTCAACCATTTTTGATGGTACTGAAGCGACCGTATCAAAGGG
AGTTGCCGATCAAAATGGTAAAGCGCTGAATGATAGTGTATCATGGGATTATCATAAAACTACTTTTACAGCAACTACACATAATT
ACAGTTATTTAAATTTAACAAATGATGCTAACGAAGTTAATATTCTAAAGTCAAGAATTCCAAAGGAAGCGGAGCATATAAATGGG
GATCGCACGCTCTATCAATTTGGTGCGACATTTACTCAAAAAGCTCTAATGAAAGCAAATGAAATTTTAGAGACACAAAGTTCTAA
TGCTAGAAAAAAACTTATTTTTCACGTAACTGATGGTGTCCCTACGATGTCTTATGCCATAAATTTTAATCCTTATATATCAACAT
CTTACCAAAACCAGTTTAATTCTTTTTTAAATAAAATACCAGATAGAAGTGGTATTCTCCAAGAGGATTTTATAATCAATGGTGAT
GATTATCAAATAGTAAAAGGAGATGGAGAGAGTTTTAAACTGTTTTCGGATAGAAAAGTTCCTGTTACTGGAGGAACGACACAAGC
AGCTTATCGAGTACCGCAAAATCAACTCTCTGTAATGAGTAATGAGGGATATGCAATTAATAGTGGATATATTTATCTCTATTGGA
GAGATTACAACTGGGTCTATCCATTTGATCCTAAGACAAAGAAAGTTTCTGCAACGAAACAAATCAAAACTCATGGTGAGCCAACA
ACATTATACTTTAATGGAAATATAAGACCTAAAGGTTATGACATTTTTACTGTTGGGATTGGTGTAAACGGAGATCCTGGTGCAAC
TCCTCTTGAAGCTGAGAAATTTATGCAATCAATATCAAGTAAAACAGAAAATTATACTAATGTTGATGATACAAATAAAATTTATG
ATGAGCTAAATAAATACTTTAAAACAATTGTTGAGGAAAAACATTCTATTGTTGATGGAAATGTGACTGATCCTATGGGAGAGATG
ATTGAATTCCAATTAAAAAATGGTCAAAGTTTTACACATGATGATTACGTTTTGGTTGGAAATGATGGCAGTCAATTAAAAAATGG
TGTGGCTCTTGGTGGACCAAACAGTGATGGGGGAATTTTAAAAGATGTTACAGTGACTTATGATAAGACATCTCAAACCATCAAAA
TCAATCATTTGAACTTAGGAAGTGGACAAAAAGTAGTTCTTACCTATGATGTACGTTTAAAAGATAACTATATAAGTAACAAATTT
TACAATACAAATAATCGTACAACGCTAAGTCCGAAGAGTGAAAAAGAACCAAATACTATTCGTGATTTCCCAATTCCCAAAATTCG
TGATGTTCGTGAGTTTCCGGTACTAACCATCAGTAATCAGAAGAAAATGGGTGAGGTTGAATTTATTAAAGTTAATAAAGACAAAC
ATTCAGAATCGCTTTTGGGAGCTAAGTTTCAACTTCAGATAGAAAAAGATTTTTCTGGGTATAAGCAATTTGTTCCAGAGGGAAGT
GATGTTACAACAAAGAATGATGGTAAAATTTATTTTAAAGCACTTCAAGATGGTAACTATAAATTATATGAAATTTCAAGTCCAGA
TGGCTATATAGAGGTTAAAACGAAACCTGTTGTGACATTTACAATTCAAAATGGAGAAGTTACGAACCTGAAAGCAGATCCAAATG
CTAATAAAAATCAAATCGGGTATCTTGAAGGAAATGGTAAACATCTTATTACCAACACTCCCAAACGCCCACCAGGTGTTTTTCCT
AAAACAGGGGGAATTGGTACAATTGTCTATATATTAGTTGGTTCTACTTTTATGATACTTACCATTTGTTCTTTCCGTCGTAAACA
ATTG

SEQ ID NO. 6

MKKRQKIWRGLSVTLLILSQIPFGILVQGETQDTNQALGKVIVKKTGDNATPLGKATFVLKNDNDKSETSHETVEGSGEATFENIK
PGDYTLREETAPIGYKKTDKTWKVKVADNGATIIEGMDADKAEKRKEVLNAQYPKSAIYEDTKENYPLVNVEGSKVGEQYKALNPI
NGKDGRREIAEGWLSKKITGVNDLDKNKYKIELTVEGKTTVETKELNQPLDVVVLLDNSNSMNNERANNSQRALKAGEAVEKLIDK
ITSNKDNRVALVTYASTIFDGTEATVSKGVADQNGKALNDSVSWDYHKTTFTATTHNYSYLNLTNDANEVNILKSRIPKEAEHING
DRTLYQFGATFTQKALMKANEILETQSSNARKKLIFHVTDGVPTMSYAINFNPYISTSYQNQFNSFLNKIPDRSGILQEDFIINGD
DYQIVKGDGESFKLFSDRKVPVTGGTTQAAYRVPQNQLSVMSNEGYAINSGYIYLYWRDYNWVYPFDPKTKKVSATKQIKTHGEPT
TLYFNGNIRPKGYDIFTVGIGVNGDPGATPLEAEKFMQSISSKTENYTNVDDTNKIYDELNKYFKTIVEEKHSIVDGNVTDPMGEM
IEFQLKNGQSFTHDDYVLVGNDGSQLKNGVALGGPNSDGGILKDVTVTYDKTSQTIKINHLNLGSGQKVVLTYDVRLKDNYISNKF
YNTNNRTTLSPKSEKEPNTIRDFPIPKIRDVREFPVLTISNQKKMGEVEFIKVNKDKHSESLLGAKFQLQIEKDFSGYKQFVPEGS
DVTTKNDGKIYFKALQDGNYKLYEISSPDGYIEVKTKPVVTFTIQNGEVTNLKADPNANKNQIGYLEGNGKHLITNTPKRPPGVFP
KTGGIGTIVYILVGSTFMILTICSFRRKQL

SEQ ID NO. 7

GTGGATAAACATCACTCAAAAAAGGCTATTTTAAAGTTAACACTTATAACAACTAGTATTTTATTAATGCATAGCAATCAAGTGAATGCAGAGGAG
CAAGAATTAAAAAACCAAGAGCAATCACCTGTAATTGCTAATGTTGCTCAACAGCCATCGCCATCGGTAACTACTAATACTGTTGAAAAAACATCT
GTAACAGCTGCTTCTGCTAGTAATACAGCGAAAGAAATGGGTGATACATCTGTAAAAAATGACAAAACAGAAGATGAATTATTAGAAGAGTTATCT
AAAAACCTTGATACGTCTAATTTGGGGGCTGATCTTGAAGAAGAATATCCCTCTAAACCAGAGACAACCAACAATAAAGAAAGCAATGTAGTAACA
AATGCTTCAACTGCAATAGCACAGAAAGTTCCCTCAGCATATGAAGAGGTGAAGCCAGAAAGCAAGTCATCGCTTGCTGTTCTTGATACATCTAAA
ATAACAAAATTACAAGCCATAACCCAAAGAGGAAAGGGAAATGTAGTAGCTATTATTGATACTGGCTTTGATATTAACCATGATATTTTTCGTTTA
GATAGCCCAAAAGATGATAAGCACAGCTTTAAAACTAAGACAGAATTTGAGGAATTAAAAGCAAAACATAATATCACTTATGGGAAATGGGTTAAC
GATAAGATTGTTTTTGCACATAACTACGCCAACAATACAGAAACGGTGGCTGATATTGCAGCAGCTATGAAAGATGGTTATGGTTCAGAAGCAAAG
AATATTTCGCATGGTACACACGTTGCTGGTATTTTTGTAGGTAATAGTAAACGTCCAGCAATCAATGGTCTTCTTTTAGAAGGTGCAGCGCCAAAT
GCTCAAGTCTTATTAATGCGTATTCCAGATAAAATTGATTCGGACAAATTTGGTGAAGCATATGCTAAAGCAATCACAGACGCTGTTAATCTAGGA

GCAAAAACGATTAATATGAGTATTGGAAAAACAGCTGATTCTTTAATTGCTCTCAATGATAAAGTTAAATTAGCACTTAAATTAGCTTCTGAGAAG
GGCGTTGCAGTTGTTGTGGCTGCCGGAAATGAAGGCGCATTTGGTATGGATTATAGCAAACCATTATCAACTAATCCTGACTACGGTACGGTTAAT
AGTCCAGCTATTTCTGAAGATACTTTGAGTGTTGCTAGCTATGAATCACTTAAAACTATCAGTGAGGTCGTTGAAACAACTATTGAAGGTAAGTTA
GTTAAGTTGCCGATTGTGACTTCTAAACCTTTTGACAAAGGTAAGGCCTACGATGTGGTTTATGCCAATTATGGTGCAAAAAAAGACTTTGAAGGT
AAGGACTTTAAAGGTAAGATTGCATTAATTGAGCGTGGTGGTGGACTTGATTTTATGACTAAAATCACTCATGCTACAAATGCAGGTGTTGTTGGT
ATCGTTATTTTTAACGATCAAGAAAAACGTGGAAATTTTCTAATTCCTTACCGTGAATTACCTGTGGGGATTATTAGTAAAGTAGATGGCGAGCGT
ATAAAAAATACTTCAAGTCAGTTAACATTTAACCAGAGTTTTGAAGTAGTTGATAGCCAAGGTGGTAATCGTATGCTGGAACAATCAAGTTGGGGC
GTGACAGCTGAAGGAGCAATCAAGCCTGATGTAACAGCTTCTGGCTTTGAAATTTATTCTTCAACCTATAATAATCAATACCAAACAATGTCTGGT
ACAAGTATGGCTTCACCACATGTTGCAGGATTAATGACAATGCTTCAAAGTCATTTGGCTGAGAAATATAAAGGGATGAATTTAGATTCTAAAAAA
TTGCTAGAATTGTCTAAAAACATCCTCATGAGCTCAGCAACAGCATTATATAGTGAAGAGGATAAGGCGTTTTATTCACCACGTCAGCAAGGTGCA
GGTGTAGTTGATGCTGAAAAAGCTATCCAAGCTCAATATTATATTACTGGAAACGATGGCAAAGCTAAAATTAATCTCAAACGAATGGGAGATAAA
TTTGATATCACAGTTACAATTCATAAACTTGTAGAAGGTGTCAAAGAATTGTATTATCAAGCTAATGTAGCAACAGAACAAGTAAATAAAGGTAAA
TTTGCCCTTAAACCACAAGCCTTGCTAGATACTAATTGGCAGAAAGTAATTCTTCGTGATAAAGAAACACAAGTTCGATTTACTATTGATGCTAGT
CAATTTAGTCAGAAATTAAAAGAACAGATGGCAAATGGTTATTTCTTAGAAGGTTTTGTACGTTTTAAAGAAGCCAAGGATAGTAATCAGGAGTTA
ATGAGTATTCCTTTTGTAGGATTTAATGGTGATTTTGCGAACTTACAAGCACTTGAAACACCGATTTATAAGACGCTTTCTAAAGGTAGTTTCTAC
TATAAACCAAATGATACAACTCATAAAGACCAATTGGAGTACAATGAATCAGCTCCTTTTGAAAGCAACAACTATACTGCCTTGTTAACACAATCA
GCGTCTTGGGGCTATGTTGATTATGTCAAAAATGGTGGGGAGTTAGAATTAGCACCGGAGAGTCCAAAAAGAATTATTTTAGGAACTTTTGAGAAT
AAGGTTGAGGATAAAACAATTCATCTTTTGGAAAGAGATGCAGCGAATAATCCATATTTTGCCATTTCTCCAAATAAAGATGGAAATAGGGACGAA
ATCACTCCCCAGGCAACTTTCTTAAGAAATGTTAAGGATATTTCTGCTCAAGTTCTAGATCAAAATGGAAATGTTATTTGGCAAAGTAAGGTTTTA
CCATCTTATCGTAAAAATTTCCATAATAATCCAAAGCAAAGTGATGGTCATTATCGTATGGATGCTCTTCAGTGGAGTGGTTTAGATAAGGATGGC
AAAGTTGTAGCAGATGGTTTTTATACTTATCGCTTACGTTACACACCAGTAGCAGAAGGAGCAAATAGTCAGGAGTCAGACTTTAAAGTACAAGTA
AGTACTAAGTCACCAAATCTTCCTTCACGAGCTCAGTTTGATGAAACTAATCGAACATTAAGCTTAGCCATGCCTAAGGAAAGTAGTTATGTTCCT
ACATATCGTTTACAATTAGTTTTATCTCATGTTGTAAAAGATGAAGAATATGGGGATGAGACTTCTTACCATTATTTCCATATAGATCAAGAAGGT
AAAGTGACACTTCCTAAAACGGTTAAGATAGGAGAGAGTGAGGTTGCGGTAGACCCTAAGGCCTTGACACTTGTTGTGGAAGATAAAGCTGGTAAT
TTCGCAACGGTAAAATTGTCTGATCTCTTGAATAAGGCAGTAGTATCAGAGAAAGAAAACGCTATAGTAATTTCTAACAGTTTCAAATATTTTGAT
AACTTGAAAAAAGAACCTATGTTTATTTCTAAAAAAGAAAAAGTAGTAAACAAGAATCTAGAAGAAATAATATTAGTTAAGCCGCAAACTACAGTT
ACTACTCAATCATTGTCTAAAGAAATAACTAAATCAGGAAATGAGAAAGTCCTCACTTCTACAAACAATAATAGTAGCAGAGTAGCTAAGATCATA
TCACCTAAACATAACGGGGATTCTGTTAACCATACCTTACCTAGTACATCAGATAGAGCAACGAATGGTCTATTTGTTGGTACTTTGGCATTGTTA
TCTAGTTTACTTCTTTATTTGAAACCCAAAAAGACTAAAAATAATAGTAAA

SEQ ID NO. 8

VDKHHSKKAILKLTLITTSILLMHSNQVNAEEQELKNQEQSPVIANVAQQPSPSVTTNTVEKTSVTAASASNTAKEMGDTSVKNDKTEDELLEELS
KNLDTSNLGADLEEEYPSKPETTNNKESNVVTNASTAIAQKVPSAYEEVKPESKSSLAVLDTSKITKLQAITQRGKGNVVAIIDTGFDINHDIFRL
DSPKDDKHSFKTKTEFEELKAKHNITYGKWVNDKIVFAHNYANNTETVADIAAAMKDGYGSEAKNISHGTHVAGIFVGNSKRPAINGLLLEGAAPN
AQVLLMRIPDKIDSDKFGEAYAKAITDAVNLGAKTINMSIGKTADSLIALNDKVKLALKLASEKGVAVVVAAGNEGAFGMDYSKPLSTNPDYGTVN
SPAISEDTLSVASYESLKTISEVVETTIEGKLVKLPIVTSKPFDKGKAYDVVYANYGAKKDFEGKDFKGKIALIERGGGLDFMTKITHATNAGVVG
IVIFNDQEKRGNFLIPYRELPVGIISKVDGERIKNTSSQLTFNQSFEVVDSQGGNRMLEQSSWGVTAEGAIKPDVTASGFEIYSSTYNNQYQTMSG
TSMASPHVAGLMTMLQSHLAEKYKGMNLDSKKLLELSKNILMSSATALYSEEDKAFYSPRQQGAGVVDAEKAIQAQYYITGNDGKAKINLKRMGDK
FDITVTIHKLVEGVKELYYQANVATEQVNKGKFALKPQALLDTNWQKVILRDKETQVRFTIDASQFSQKLKEQMANGYFLEGFVRFKEAKDSNQEL
MSIPFVGFNGDFANLQALETPIYKTLSKGSFYYKPNDTTHKDQLEYNESAPFESNNYTALLTQSASWGYVDYVKNGGELELAPESPKRIILGTFEN
KVEDKTIHLLERDAANNPYFAISPNKDGNRDEITPQATFLRNVKDISAQVLDQNGNVIWQSKVLPSYRKNFHNNPKQSDGHYRMDALQWSGLDKDG
KVVADGFYTYRLRYTPVAEGANSQESDFKVQVSTKSPNLPSRAQFDETNRTLSLAMPKESSYVPTYRLQLVLSHVVKDEEYGDETSYHYFHIDQEG
KVTLPKTVKIGESEVAVDPKALTLVVEDKAGNFATVKLSDLLNKAVVSEKENAIVISNSFKYFDNLKKEPMFISKKEKVVNKNLEEIILVKPQTTV
TTQSLSKEITKSGNEKVLTSTNNNSSRVAKIISPKHNGDSVNHTLPSTSDRATNGLFVGTLALLSSLLLYLKPKKTKNNSK

SEQ ID NO. 9

ATGAAACGTAAATACTTTATTCTTAATACGGTGACGGTTTTAACGTTAGCTGCTGCAATGAATACTAGCAGTATCTATGCTAATAGTACTGAGACA
AGTGCTTCAGTAGTTCCTACTACAAATACTATCGTTCAAACTAATGACAGTAATCCTACCGCAAAATTTGTATCAGAATCAGGACAATCTGTAATA
GGTCAAGTAAAACCAGATAATTCTGCGGCGCTTACAACAGTTGACACGCCTCATCATATTTCAGCTCCAGATGCTTTAAAAACAACTCAATCAAGT
CCTGTCGTTGAGAGTACTTCTACTAAGTTAACTGAAGAGACTTACAAACAAAAAGATGGTCAAGATTTAGCCAACATGGTGAGAAGTGGTCAAGTT
ACTAGTGAGGAACTCGTTAATATGGCATACGATATTATTGCTAAAGAAAACCCATCTTTAAATGCAGTCATTACTACTAGACGCCAAGAAGCTATT
GAAGAGGCTAGAAAACTTAAAGATACCAATCAGCCGTTTTTAGGTGTTCCCTTGTTAGTCAAGGGGTTAGGGCACAGTATTAAAGGTGGTGAAACC
AATAATGGCTTGATCTATGCAGATGGAAAAATTAGCACATTTGACAGTAGCTATGTCAAAAAATATAAAGATTTAGGATTTATTATTTTAGGACAA
ACGAACTTTCCAGAGTATGGGTGGCGTAATATAACAGATTCTAAATTATACGGTCTAACGCATAATCCTTGGGATCTTGCTCATAATGCTGGTGGC
TCTTCTGGTGGAAGTGCAGCAGCCATTGCTAGCGGAATGACGCCAATTGCTAGCGGTAGTGATGCTGGTGGTTCTATCCGTATTCCATCTTCTTGG
ACGGGCTTGGTAGGTTTAAAACCAACAAGAGGATTGGTGAGTAATGAAAAGCCAGATTCGTATAGTACAGCAGTTCATTTTCCATTAACTAAGTCA
TCTAGAGACGCAGAAACATTATTAACTTATCTAAAGAAAAGCGATCAAACGCTAGTATCAGTTAATGATTTAAAATCTTTACCAATTGCTTATACT
TTGAAATCACCAATGGGAACAGAAGTTAGTCAAGATGCTAAAAACGCTATTATGGACAACGTCACATTCTTAAGAAAACAAGGATTCAAAGTAACA
GAGATAGACTTACCAATTGATGGTAGAGCATTAATGCGTGATTATTCAACCTTGGCTATTGGCATGGGAGGAGCTTTTTCAACAATTGAAAAAGAC
TTAAAAAAACATGGTTTTACTAAAGAAGACGTTGATCCTATTACTTGGGCAGTTCATGTTATTTATCAAAATTCAGATAAGGCTGAACTTAAGAAA
TCTATTATGGAAGCCCAAAAACATATGGATGATTATCGTAAGGCAATGGAGAAGCTTCACAAGCAATTTCCTATTTTCTTATCGCCAACGACCGCA
AGTTTAGCCCCTCTAAATACAGATCCATATGTAACAGAGGAAGATAAAAGAGCGATTTATAATATGGAAAACTTGAGCCAAGAAGAAAGAATTGCT
CTCTTTAATCGCCAGTGGGAGCCTATGTTGCGTAGAACACCTTTTACACAAATTGCTAATATGACAGGACTCCCAGCTATCAGTATCCCGACTTAC
TTATCTGAGTCTGGTTTACCCATAGGGACGATGTTAATGGCAGGTGCAAACTATGATATGGTATTAATTAAATTTGCAACTTTCTTTGAAAAACAT
CATGGTTTTAATGTTAAATGGCAAAGAATAATAGATAAAGAAGTGAAACCATCTACTGGCCTAATACAGCCTACTAACTCCCTCTTTAAAGCTCAT
TCATCATTAGTAAATTTAGAAGAAAATTCACAAGTTACTCAAGTATCTATCTCTAAAAAATGGATGAAATCGTCTGTTAAAAATAAACCATCCGTA
ATGGCATATCAAAAAGCACTTCCTAAAACAGGTGATACAGAATCAAGCCTATCTCCAGTTTTAGTAGTAACCCTTTTATTAGCTTGTTTTAGCTTT
GTAACAAAAAAGAATCAGAAAAGT

SEQ ID NO. 10

MKRKYFILNTVTVLTLAAAMNTSSIYANSTETSASVVPTTNTIVQTNDSNPTAKFVSESGQSVIGQVKPDNSAALTTVDTPHHISAPDALKTTQSS
PVVESTSTKLTEETYKQKDGQDLANMVRSGQVTSEELVNMAYDIIAKENPSLNAVITTRRQEAIEEARKLKDTNQPFLGVPLLVKGLGHSIKGGET
NNGLIYADGKISTFDSSYVKKYKDLGFIILGQTNFPEYGWRNITDSKLYGLTHNPWDLAHNAGGSSGGSAAAIASGMTPIASGSDAGGSIRIPSSW
TGLVGLKPTRGLVSNEKPDSYSTAVHFPLTKSSRDAETLLTYLKKSDQTLVSVNDLKSLPIAYTLKSPMGTEVSQDAKNAIMDNVTFLRKQGFKVT
EIDLPIDGRALMRDYSTLAIGMGGAFSTIEKDLKKHGFTKEDVDPITWAVHVIYQNSDKAELKKSIMEAQKHMDDYRKAMEKLHKQFPIFLSPTTA
SLAPLNTDPYVTEEDKRAIYNMENLSQEERIALFNRQWEPMLRRTPFTQIANMTGLPAISIPTYLSESGLPIGTMLMAGANYDMVLIKFATFFEKH
HGFNVKWQRIIDKEVKPSTGLIQPTNSLFKAHSSLVNLEENSQVTQVSISKKWMKSSVKNKPSVMAYQKALPKTGDTESSLSPVLVVTLLLACFSF
VTKKNQKS

SEQ ID NO. 11

TTGCGTAAAAAACAAAAACTACCATTTGATAAACTTGCCATTGCGCTTATATCTACGAGCATCTTGCTCAATGCACAATCAGACATTAAAGCAAAT
ACTGTGACAGAAGACACTCCTGCTACCGAACAAGCCGTAGAACCCCCACAACCAATAGCAGTTTCTGAGGAATCACGATCATCAAAGGAAACTAAA
ACCTCACAAACTCCTAGTGATGTAGGAGAAACAGTAGCAGATGACGCTAATGATCTAGCCCCTCAAGCTCCTGCTAAAACTGCTGATACACCAGCA
ACCTCAAAAGCGACTATTAGGGATTTGAACGACCCTTCTCATGTCAAAACCCTGCAGGAAAAAGCAGGCAAGGGAGCTGGGACCGTTGTTGCAGTG
ATTGATGCTGGTTTTGATAAAAATCATGAAGCGTGGCGCTTAACAGACAAAACTAAAGCACGTTACCAATCAAAAGAAAATCTTGAAAAAGCTAAA
AAAGAGCACGGTATTACCTATGGCGAGTGGGTCAATGATAAGGTTGCTTATTACCACGACTATAGTAAAGATGGTAAAAACGCTGTTGATCAAGAA
CACGGCACACACGTGTCAGGGATCTTGTCAGGAAATGCTCCATCTGAAATGAAAGAACCTTACCGCCTAGAAGGTGCGATGCCTGAGGCTCAATTG
CTTTTGATGCGTGTCGAAATTGTAAATGGACTAGCAGACTATGCTCGTAACTACGCTCAAGCTATCAGAGATGCTGTCAACTTGGGAGCTAAGGTG
ATTAATATGAGCTTTGGTAATGCTGCACTAGCTTACGCCAACCTTCCAGACGAAACCAAAAAAGCCTTTGACTATGCCAAATCAAAAGGTGTTAGC
ATTGTGACCTCAGCTGGTAATGATAGTAGCTTTGGGGGCAAGCCCCGTCTACCTCTAGCAGATCATCCTGATTATGGGGTGGTTGGGACACCTGCA
GCGGCAGATTCAACATTGACAGTTGCTTCTTACAGCCCAGATAAACAGCTCACTGAAACTGCTACGGTCAAAACAGACGATCATCAAGATAAAGAA
ATGCCTGTTATTTCAACAAACCGTTTTGAGCCAAACAAGGCTTACGACTATGCTTATGCTAATCGTGGTACGAAAGAGGATGATTTTAAGGATGTC
GAAGGTAAGATTGCCCTTATTGAACGTGGCGATATTGATTTCAAAGATAAGATTGCAAACGCTAAAAAAGCTGGTGCTGTAGGGGTCTTGATCTAT
GACAATCAAGACAAGGGCTTCCCGATTGAATTGCCAAATGTTGACCAGATGCCTGCGGCCTTTATCAGTCGAAGAGACGGTCTCTTATTAAAAGAC
AATCCCCCAAAAACCATTACCTTCAATGCGACACCTAAGGTATTGCCAACAGCAAGTGGCACCAAACTAAGCCGCTTCTCAAGCTGGGGTCTGACA
GCTGACGGCAATATTAAACCGGATATTGCAGCACCCGGCCAAGATATTTTGTCATCAGTGGCTAACAACAAGTATGCCAAACTTTCTGGAACTAGT
ATGTCTGCACCATTGGTAGCGGGTATCATGGGACTGTTGCAAAAGCAATATGAGACACAGTATCCTGATATGACACCATCAGAGCGTCTTGATTTA
GCTAAGAAAGTATTGATGAGCTCAGCAACTGCCCTATATGATGAAGATGAAAAAGCTTATTTTTCTCCTCGCCAACAGGGAGCAGGAGCAGTCGAT
GCTAAAAAAGCTTCAGCAGCAACGATGTATGTAACAGATAAGGACAATACCTCAAGCAAGGTTCACCTGAACAATGTTTCTGATAAATTTGAAGTA
ACAGTAACAGTTCACAACAAATCTGATAAACCTCAAGAGTTGTATTACCAAGTAACTGTTCAAACAGATAAAGTAGATGGAAAACACTTTGCCTTG
GCTCCTAAAGCATTGTATGAGACATCATGGCAAAAAATCACAATTCCAGCCAATAGCAGCAAACAAGTCACCGTTCCAATCGATGCTAGTCGATTT
AGCAAGGACTTGCTTGCCCAAATGAAAAATGGCTATTTCTTAGAAGGTTTTGTTCGTTTCAAACAAGATCCTACAAAAGAAGAGCTTATGAGCATT
CCATATATTGGTTTCCGAGGTGATTTTGGCAATCTGTCAGCCTTAGAAAAACCAATCTATGATAGCAAAGACGGTAGCAGCTACTATCATGAAGCA
AATAGTGATGCCAAAGACCAATTAGATGGTGATGGATTACAGTTTTACGCTCTGAAAAATAACTTTACAGCACTTACCACAGAGTCTAACCCATGG
ACGATTATTAAAGCTGTCAAAGAAGGGGTTGAAAACATAGAGGATATCGAATCTTCAGAGATCACAGAAACCATTTTTGCAGGTACTTTTGCAAAA
CAAGACGATGATAGCCACTACTATATCCACCGTCACGCTAATGGCAAACCATATGCTGCGATCTCTCCAAATGGGGACGGTAACAGAGATTATGTC
CAATTCCAAGGTACTTTCTTGCGTAATGCTAAAAACCTTGTGGCTGAAGTCTTGGACAAAGAAGGAAATGTTGTTTGGACAAGTGAGGTAACCGAG
CAAGTTGTTAAAAACTACAACAATGACTTGGCAAGCACACTTGGTTCAACCCGTTTTGAAAAAACGCGTTGGGACGGTAAAGATAAAGACGGCAAA
GTTGTTGCTAACGGAACCTACACCTATCGTGTTCGCTACACGCCGATTAGCTCAGGTGCAAAAGAACAACACACTGATTTTGATGTGATTGTAGAC
AATACGACACCTGAAGTCGCAACATCGGCAACATTCTCAACAGAAGATAGTCGTTTGACACTTGCATCTAAACCAAAAACCAGCCAACCGGTTTAC
CGTGAGCGTATTGCTTACACTTATATGGATGAGGATCTGCCAACAACAGAGTATATTTCTCCAAATGAAGATGGTACCTTTACTCTTCCTGAAGAG
GCTGAAACAATGGAAGGCGCTACTGTTCCATTGAAAATGTCAGACTTTACTTATGTTGTTGAAGATATGGCTGGTAACATCACTTATACACCAGTG
ACTAAGCTATTGGAGGGCCACTCTAATAAGCCAGAACAAGACGGTTCAGATCAAGCACCAGACAAGAAACCAGAAGCTAAACCAGAACAAGACGGT
TCAGGTCAAACACCAGATAAAAAAAAAGAAACTAAACCAGAAAAAGATAGTTCAGGTCAAACACCAGGTAAAACTCCTCAAAAAGGTCAATCTTCT
CGTACTCTAGAGAAACGATCTTCTAAGCGTGCTTTAGCTACAAAAGCATCAACAAGAGATCAGTTACCAACGACTAATGACAAGGATACAAATCGT
TTACATCTCCTTAAGTTAGTTATGACCACTTTCTTCTTGGGA

SEQ ID NO. 12

MRKKQKLPFDKLAIALISTSILLNAQSDIKANTVTEDTPATEQAVEPPQPIAVSEESRSSKETKTSQTPSDVGETVADDANDLAPQ
APAKTADTPATSKATIRDLNDPSHVKTLQEKAGKGAGTVVAVIDAGFDKNHEAWRLTDKTKARYQSKENLEKAKKEHGITYGEWVN
DKVAYYHDYSKDGKNAVDQEHGTHVSGILSGNAPSEMKEPYRLEGAMPEAQLLLMRVEIVNGLADYARNYAQAIRDAVNLGAKVIN
MSFGNAALAYANLPDETKKAFDYAKSKGVSIVTSAGNDSSFGGKPRLPLADHPDYGVVGTPAAADSTLTVASYSPDKQLTETATVK
TDDHQDKEMPVISTNRFEPNKAYDYAYANRGTKEDDFKDVEGKIALIERGDIDFKDKIANAKKAGAVGVLIYDNQDKGFPIELPNV
DQMPAAFISRRDGLLLKDNPPKTITFNATPKVLPTASGTKLSRFSSWGLTADGNIKPDIAAPGQDILSSVANNKYAKLSGTSMSAP
LVAGIMGLLQKQYETQYPDMTPSERLDLAKKVLMSSATALYDEDEKAYFSPRQQGAGAVDAKKASAATMYVTDKDNTSSKVHLNNV
SDKFEVTVTVHNKSDKPQELYYQVTVQTDKVDGKHFALAPKALYETSWQKITIPANSSKQVTVPIDASRFSKDLLAQMKNGYFLEG
FVRFKQDPTKEELMSIPYIGFRGDFGNLSALEKPIYDSKDGSSYYHEANSDAKDQLDGDGLQFYALKNNFTALTTESNPWTIIKAV
KEGVENIEDIESSEITETIFAGTFAKQDDDSHYYIHRHANGKPYAAISPNGDGNRDYVQFQGTFLRNAKNLVAEVLDKEGNVVWTS
EVTEQVVKNYNNDLASTLGSTRFEKTRWDGKDKDGKVVANGTYTYRVRYTPISSGAKEQHTDFDVIVDNTTPEVATSATFSTEDSR
LTLASKPKTSQPVYRERIAYTYMDEDLPTTEYISPNEDGTFTLPEEAETMEGATVPLKMSDFTYVVEDMAGNITYTPVTKLLEGHS
NKPEQDGSDQAPDKKPEAKPEQDGSGQTPDKKKETKPEKDSSGQTPGKTPQKGQSSRTLEKRSSKRALATKASTRDQLPTTNDKDT
NRLHLLKLVMTTFFLG

SEQ ID NO. 13

ATGGGACGAGTAATGAAAACAATAACAACATTTGAAAATAAAAAAGTTTTAGTCCTTGGTTTAGCACGATCTGGAGAAGCTGCTGC
ACGTTTGTTAGCTAAGTTAGGAGCAATAGTGACAGTTAATGATGGCAAACCATTTGATGAAAATCCAACAGCACAGTCTTTGTTGG
AAGAGGGTATTAAAGTGGTTTGTGGTAGTCATCCTTTAGAATTGTTAGATGAGGATTTTTGTTACATGATTAAAAATCCAGGAATA
CCTTATAACAATCCTATGGTCAAAAAAGCATTAGAAAAACAAATCCCTGTTTTGACTGAAGTGGAATTAGCATACTTAGTTTCAGA
ATCTCAGCTAATAGGTATTACAGGCTCTAACGGGAAAACGACAACGACAACGATGATTGCAGAAGTCTTAAATGCTGGAGGTCAGA
GAGGTTTGTTAGCTGGGAATATCGGCTTTCCTGCTAGTGAAGTTGTTCAGGCTGCGAATGATAAAGATACTCTAGTTATGGAATTA
TCAAGTTTTCAGCTAATGGGAGTTAAGGAATTTCGTCCTCATATTGCAGTAATTACTAATTTAATGCCAACTCATTTAGATTATCA
TGGGTCTTTTGAAGATTATGTTGCTGCAAAATGGAATATCCAAAATCAAATGTCTTCATCTGATTTTTTGGTACTTAATTTTAATC
AAGGTATTTCTAAAGAGTTAGCTAAAACTACTAAAGCAACAATCGTTCCTTTCTCTACTACGGAAAAAGTTGATGGTGCTTACGTA
CAAGACAAGCAACTTTTCTATAAAGGGGAGAATATTATGTCAGTAGATGACATTGGTGTCCCAGGAAGCCATAACGTAGAGAATGC
TCTAGCAACTATTGCGGTTGCTAAACTGGCTGGTATCAGTAATCAAGTTATTAGAGAAACTTTAAGCAATTTTGGAGGTGTTAAAC
ACCGCTTGCAATCACTCGGTAAGGTTCATGGTATTAGTTTCTATAACGACAGCAAGTCAACTAATATATTGGCAACTCAAAAAGCA
TTATCTGGCTTTGATAATACTAAAGTTATCCTAATTGCAGGAGGTCTTGATCGCGGTAATGAGTTTGATGAATTGATACCAGATAT
CACTGGACTTAAACATATGGTTGTTTTAGGGGAATCGGCATCTCGAGTAAAACGTGCTGCACAAAAAGCAGGAGTAACTTATAGCG
ATGCTTTAGATGTTAGAGATGCGGTACATAAAGCTTATGAGGTGGCACAACAGGGCGATGTTATCTTGCTAAGTCCTGCAAATGCA
TCATGGGACATGTATAAGAATTTCGAAGTCCGTGGTGATGAATTCATTGATACTTTCGAAAGTCTTAGAGGAGAG

SEQ ID NO. 14

MGRVMKTITTFENKKVLVLGLARSGEAAARLLAKLGAIVTVNDGKPFDENPTAQSLLEEGIKVVCGSHPLELLDEDFCYMIKNPGI
PYNNPMVKKALEKQIPVLTEVELAYLVSESQLIGITGSNGKTTTTTMIAEVLNAGGQRGLLAGNIGFPASEVVQAANDKDTLVMEL
SSFQLMGVKEFRPHIAVITNLMPTHLDYHGSFEDYVAAKWNIQNQMSSSDFLVLNFNQGISKELAKTTKATIVPFSTTEKVDGAYV
QDKQLFYKGENIMSVDDIGVPGSHNVENALATIAVAKLAGISNQVIRETLSNFGGVKHRLQSLGKVHGISFYNDSKSTNILATQKA
LSGFDNTKVILIAGGLDRGNEFDELIPDITGLKHMVVLGESASRVKRAAQKAGVTYSDALDVRDAVHKAYEVAQQGDVILLSPANA
SWDMYKNFEVRGDEFIDTFESLRGE

SEQ ID NO. 15

ATGAAACGTATTGCTGTTTTAACTAGTGGTGGTGACGCCCCTGGTATGAACGCTGCTATCCGTGCAGTTGTTCGTAAAGCAATTTCTGAAGGTATG
GAAGTTTACGGCATCAACCAAGGTTACTATGGTATGGTGACAGGGGATATTTTCCCTTTGGATGCTAATTCTGTTGGGGATACTATCAACCGTGGA
GGAACGTTTTTACGTTCAGCACGTTATCCTGAATTTGCTGAACTTGAAGGTCAGCTTAAAGGGATTGAACAGCTTAAAAAACACGGTATTGAAGGT
GTAGTAGTTATCGGTGGTGATGGTTCTTATCATGGTGCTATGCGTCTAACTGAGCACGGTTTCCCAGCTGTTGGTTTGCCGGGTACAATTGATAAC
GATATCGTTGGCACTGACTATACTATTGGTTTTGACACAGCAGTTGCGACAGCAGTTGAGAATCTTGACCGTCTTCGTGATACATCAGCAAGTCAT
AACCGTACTTTTGTTGTTGAGGTTATGGGAAGAAATGCAGGAGATATCGCTCTTTGGTCAGGTATCGCTGCAGGTGCAGATCAAATTATTGTTCCT
GAAGAAGAGTTCAATATTGATGAAGTTGTCTCAAATGTTAGAGCTGGCTATGCAGCTGGTAAACATCACCAAATCATCGTCCTTGCAGAAGGTGTT
ATGAGTGGTGATGAGTTTGCAAAAACAATGAAAGCAGCAGGAGACGATAGCGATCTTCGTGTGACGAATTTAGGACATCTGCTCCGTGGTGGTAGT
CCGACGGCTCGTGATCGTGTCTTAGCATCTCGTATGGGAGCGTACGCTGTTCAATTGTTGAAAGAAGGTCGTGGTGGTTTAGCCGTTGGTGTCCAC
AACGAAGAAATGGTTGAAAGTCCAATTTTAGGTTTAGCAGAAGAAGGTGCTTTGTTCAGCTTGACTGATGAAGGAAAAATCGTTGTTAATAATCCG
CATAAAGCGGACCTTCGCTTGGCAGCACTTAATCGTGACCTTGCCAACCAAAGTAGTAAA

SEQ ID NO. 16

MKRIAVLTSGGDAPGMNAAIRAVVRKAISEGMEVYGINQGYYGMVTGDIFPLDANSVGDTINRGGTFLRSARYPEFAELEGQLKGIEQLKKHGIEG
VVVIGGDGSYHGAMRLTEHGFPAVGLPGTIDNDIVGTDYTIGFDTAVATAVENLDRLRDTSASHNRTFVVEVMGRNAGDIALWSGIAAGADQIIVP
EEEFNIDEVVSNVRAGYAAGKHHQIIVLAEGVMSGDEFAKTMKAAGDDSDLRVTNLGHLLRGGSPTARDRVLASRMGAYAVQLLKEGRGGLAVGVH
NEEMVESPILGLAEEGALFSLTDEGKIVVNNPHKADLRLAALNRDLANQSSK

SEQ ID NO. 17

ATGAATAAAAAGGTACTATTGACATCGACAATGGCAGCTTCGCTATTATCAGTCGCAAGTGTTCAAGCACAAGAAACAGATACGACGTGGACAGCA
CGTACTGTTTCAGAGGTAAAGGCTGATTTGGTAAAGCAAGACAATAAATCATCATATACTGTGAAATATGGTGATACACTAAGCGTTATTTCAGAA
GCAATGTCAATTGATATGAATGTCTTAGCAAAAATAAATAACATTGCAGATATCAATCTTATTTATCCTGAGACAACACTGACAGTAACTTACGAT
CAGAAGAGTCATACTGCCACTTCAATGAAAATAGAAACACCAGCAACAAATGCTGCTGGTCAAACAACAGCTACTGTGGATTTGAAAACCAATCAA
GTTTCTGTTGCAGACCAAAAAGTTTCTCTCAATACAATTTCGGAAGGTATGACACCAGAAGCAGCAACAACGATTGTTTCGCCAATGAAGACATAT
TCTTCTGCGCCAGCTTTGAAATCAAAAGAAGTATTAGCACAAGAGCAAGCTGTTAGTCAAGCAGCAGCTAATGAACAGGTATCACCAGCTCCTGTG
AAGTCGATTACTTCAGAAGTTCCAGCAGCTAAAGAGGAAGTTAAACCAACTCAGACGTCAGTCAGTCAGTCAACAACAGTATCACCAGCTTCTGTT
GCCGCTGAAACACCAGCTCCAGTAGCTAAAGTAGCACCGGTAAGAACTGTAGCAGCCCCTAGAGTGGCAAGTGTTAAAGTAGTCACTCCTAAAGTA
GAAACTGGTGCATCACCAGAGCATGTATCAGCTCCAGCAGTTCCTGTGACTACGACTTCACCAGCTACAGACAGTAAGTTACAAGCGACTGAAGTT
AAGAGCGTTCCGGTAGCACAAAAAGCTCCAACAGCAACACCGGTAGCACAACCAGCTTCAACAACAAATGCAGTAGCTGCACATCCTGAAAATGCA
GGGCTCCAACCTCATGTTGCAGCTTATAAAGAAAAAGTAGCGTCAACTTATGGAGTTAATGAATTCAGTACATACCGTGCGGGAGATCCAGGTGAT
CATGGTAAAGGTTTAGCAGTTGACTTTATTGTAGGTACTAATCAAGCACTTGGTAATAAAGTTGCACAGTACTCTACACAAAATATGGCAGCAAAT
AACATTTCATATGTTATCTGGCAACAAAAGTTTTACTCAAATACAAACAGTATTTATGGACCTGCTAATACTTGGAATGCAATGCCAGATCGTGGT
GGCGTTACTGCCAACCACTATGACCACGTTCACGTATCATTTAACAAATAATATAAAAAAGGAAGCTATTTGGCTTCTTTTTTATATGCCTTGAAT
AGACTTTCAAGGTTCTTATATAATTTTTATTA

SEQ ID NO. 18

MNKKVLLTSTMAASLLSVASVQAQETDTTWTARTVSEVKADLVKQDNKSSYTVKYGDTLSVISEAMSIDMNVLAKINNIADINLIYPETTLTVTYD
QKSHTATSMKIETPATNAAGQTTATVDLKTNQVSVADQKVSLNTISEGMTPEAATTIVSPMKTYSSAPALKSKEVLAQEQAVSQAAANEQVSPAPV
KSITSEVPAAKEEVKPTQTSVSQSTTVSPASVAAETPAPVAKVAPVRTVAAPRVASVKVVTPKVETGASPEHVSAPAVPVTTTSPATDSKLQATEV
KSVPVAQKAPTATPVAQPASTTNAVAAHPENAGLQPHVAAYKEKVASTYGVNEFSTYRAGDPGDHGKGLAVDFIVGTNQALGNKVAQYSTQNMAAN
NISYVIWQQKFYSNTNSIYGPANTWNAMPDRGGVTANHYDHVHVSFNK

SEQ ID NO. 19

ATGAAAAAGAAAATTATTTTGAAAAGTAGTGTTCTTGGTTTAGTCGCTGGGACTTCTATTATGTTCTCAAGCGTGTTCGCGGACCAAGTCGGTGTC
CAAGTTATAGGCGTCAATGACTTTCATGGTGCACTTGACAATACTGGAACAGCAAATATGCCTGATGGAAAAGTTGCTAATGCTGGTACTGCTGCT
CAATTAGATGCTTATATGGATGACGCTCAAAAAGATTTCAAACAAACTAACCCTAATGGTGAAAGCATTAGGGTTCAAGCAGGCGATATGGTTGGA
GCAAGTCCAGCCAACTCTGGGCTTCTTCAAGATGAACCAACTGTCAAAAATTTTAATGCAATGAATGTTGAGTATGGCACATTGGGTAACCATGAA
TTTGATGAAGGGTTGGCAGAATATAATCGTATCGTTACTGGTAAAGCCCCTGCTCCAGATTCTAATATTAATAATATTACGAAATCATACCCACAT
GAAGCTGCAAAACAAGAAATTGTAGTGGCAAATGTTATTGATAAAGTTAACAAACAAATTCCTTACAATTGGAAGCCTTACGCTATTAAAAATATT
CCTGTAAATAACAAAAGTGTGAACGTTGGCTTTATCGGGATTGTCACCAAAGACATCCCAAACCTTGTCTTACGTAAAAATTATGAACAATATGAA
TTTTTAGATGAAGCTGAAACAATCGTTAAATACGCCAAAGAATTACAAGCTAAAAATGTCAAAGCTATTGTAGTTCTCGCACATGTACCTGCAACA
AGTAAAAATGATATTGCTGAAGGTGAAGCAGCAGAAATGATGAAAAAAGTCAATCAACTCTTCCCTGAAAATAGCGTAGATATTGTCTTTGCTGGA
CACAATCATCAATATACAAATGGTCTTGTTGGTAAAACTCGTATTGTACAAGCGCTCTCTCAAGGAAAAGCCTATGCTGATGTACGTGGTGTCTTA
GATACTGATACACAAGATTTCATTGAGACCCCTTCAGCTAAAGTAATTGCAGTTGCTCCTGGTAAAAAAACAGGTAGTGCCGATATTCAAGCCATT
GTTGACCAAGCTAATACTATCGTTAAACAAGTAACAGAAGCTAAAATTGGTACTGCCGAGGTAAGTGTCATGATTACGCGTTCTGTTGATCAAGAT
AATGTTAGTCCGGTAGGCAGCCTCATCACAGAGGCTCAACTAGCAATTGCTCGAAAAAGCTGGCCAGATATCGATTTTGCCATGACAAATAATGGT
GGCATTCGTGCTGACTTACTCATCAAACCAGATGGAACAATCACCTGGGGAGCTGCACAAGCAGTTCAACCTTTTGGTAATATCTTACAAGTCGTC
GAAATTACTGGTAGAGATCTTTATAAAGCACTCAACGAACAATACGACCAAAAACAAAATTTCTTCCTTCAAATAGCTGGTCTGCGATACACTTAC
ACAGATAATAAAGAGGGCGGGGAAGAAACACCATTTAAAGTTGTAAAAGCTTATAAATCAAATGGTGAGGAAATCAATCCTGATGCAAAATACAAA
TTAGTTATCAATGACTTTTTATTCGGTGGTGGTGATGGCTTTGCAAGCTTCAGAAATGCCAAACTTCTAGGAGCCATTAACCCCGATACAGAGGTA
TTTATGGCCTATATCACTGATTTAGAAAAAGCTGGTAAAAAAGTGAGCGTTCCAAATAATAAACCTAAAATCTATGTCACTATGAAGATGGTTAAT
GAAACTATTACACAAAATGATGGTACACATAGCATTATTAAGAAACTTTATTTAGATCGACAAGGAAATATTGTAGCACAAGAGATTGTATCAGAC
ACTTTAAACCAAACAAAATCAAAATCTACAAAAATCAACCCTGTAACTACAATTCACAAAAAACAATTACACCAATTTACAGCTATTAACCCTATG
AGAAATTATGGCAAACCATCAAACTCCACTACTGTAAAATCAAAACAATTACCAAAAACAAACTCTGAATATGGACAATCATTCCTTATGTCTGTC
TTTGGTGTTGGACTTATAGGAATTGCTTTAAATACAAAGAAAAAACATATGAAA

SEQ ID NO. 20

MKKKIILKSSVLGLVAGTSIMFSSVFADQVGVQVIGVNDFHGALDNTGTANMPDGKVANAGTAAQLDAYMDDAQKDFKQTNPNGESIRVQAGDMVG
ASPANSGLLQDEPTVKNFNAMNVEYGTLGNHEFDEGLAEYNRIVTGKAPAPDSNINNITKSYPHEAAKQEIVVANVIDKVNKQIPYNWKPYAIKNI
PVNNKSVNVGFIGIVTKDIPNLVLRKNYEQYEFLDEAETIVKYAKELQAKNVKAIVVLAHVPATSKNDIAEGEAAEMMKKVNQLFPENSVDIVFAG
HNHQYTNGLVGKTRIVQALSQGKAYADVRGVLDTDTQDFIETPSAKVIAVAPGKKTGSADIQAIVDQANTIVKQVTEAKIGTAEVSVMITRSVDQD
NVSPVGSLITEAQLAIARKSWPDIDFAMTNNGGIRADLLIKPDGTITWGAAQAVQPFGNILQVVEITGRDLYKALNEQYDQKQNFFLQIAGLRYTY
TDNKEGGEETPFKVVKAYKSNGEEINPDAKYKLVINDFLFGGGDGFASFRNAKLLGAINPDTEVFMAYITDLEKAGKKVSVPNNKPKIYVTMKMVN
ETITQNDGTHSIIKKLYLDRQGNIVAQEIVSDTLNQTKSKSTKINPVTTIHKKQLHQFTAINPMRNYGKPSNSTTVKSKQLPKTNSEYGQSFLMSV
FGVGLIGIALNTKKKHMK

SEQ ID NO. 21

ATGAATAAACGCGTAAAAATCGTTGCAACACTTGGTCCTGCGGTTGAATTCCGTGGTGGTAAGAAGTTTGGTGAGTCTGGATACTGGGGTGAAAGC
CTTGACGTAGAAGCTTCAGCAGAAAAAATTGCTCAATTGATTAAAGAAGGTGCTAACGTTTTCCGTTTCAACTTCTCACATGGAGATCATGCTGAG
CAAGGAGCTCGTATGGCTACTGTTCGTAAAGCAGAAGAGATTGCAGGACAAAAAGTTGGCTTCCTCCTTGATACTAAAGGACCTGAAATTCGTACA
GAACTTTTTGAAGATGGTGCAGATTTCCATTCATATACAACAGGTACAAAATTACGTGTTGCTACTAAGCAAGGTATCAAATCAACTCCAGAAGTG
ATTGCATTGAATGTTGCTGGTGGACTTGACATCTTTGATGACGTTGAAGTTGGTAAGCAAATCCTTGTTGATGATGGTAAACTAGGTCTTACTGTG
TTTGCAAAAGATAAAGACACTCGTGAATTTGAAGTAGTTGTTGAGAATGATGGCCTTATTGGTAAACAAAAAGGTGTAAACATCCCTTATACTAAA
ATTCCTTTCCCAGCACTTGCAGAACGCGATAATGCTGATATCCGTTTTGGACTTGAGCAAGGACTTAACTTTATTGCTATCTCATTTGTACGTACT
GCTAAAGATGTTAATGAAGTTCGTGCTATTTGTGAAGAAACTGGSMATGGACACGTTAAGTTGTTTGCTAAAATTGAAAATCAACAAGGTATCGAT
AATATTGATGAGATTATCGAAGCAGCAGATGGTATTATGATTGCTCGTGGTGATATGGGTATCGAAGTTCCATTTGAAATGGTTCCAGTTTACCAA
AAAATGATCATTACTAAAGTTAATGCAGCTGGTAAAGCAGTTATTACAGCAACAAATATGCTTGAAACAATGACTGATAAACCACGTGCGACTCGT
TCAGAAGTATCTGATGTCTTCAATGCTGTTATTGATGGTACTGATGCTACAATGCTTTCAGGTGAGTCAGCTAATGGTAAATACCCAGTTGAGTCA
GTTCGTACAATGGCTACTATTGATAAAAATGCTCAAACATTACTCAATGAGTATGGTCGCTTAGACTCATCTGCATTCCCACGTAATAACAAAACT
GATGTTATTGCATCTGCGGTTAAAGATGCAACACACTCAATGGATATCAAACTTGTTGTAACAATTACTGAAACAGGTAATACAGCTCGTGCCATT
TCTAAATTCCGTCCAGATGCAGACATTTTGGCTGTTACATTTGATGAAAAAGTACAACGTTCATTGATGATTAACTGGGGTGTTATCCCTGTCCTT
GCAGACAAACCAGCATCTACAGATGATATGTTTGAGGTTGCAGAACGTGTAGCACTTGAAGCAGGATTTGTTGAATCAGGCGATAATATCGTTATC
GTTGCAGGTGTTCCTGTAGGTACAGGTGGAACTAACACAATGCGTGTTCGTACTGTTAAA

SEQ ID NO. 22

MNKRVKIVATLGPAVEFRGGKKFGESGYWGESLDVEASAEKIAQLIKEGANVFRFNFSHGDHAEQGARMATVRKAEEIAGQKVGFLLDTKGPEIRT
ELFEDGADFHSYTTGTKLRVATKQGIKSTPEVIALNVAGGLDIFDDVEVGKQILVDDGKLGLTVFAKDKDTREFEVVVENDGLIGKQKGVNIPYTK

IPFPALAERDNADIRFGLEQGLNFIAISFVRTAKDVNEVRAICEETGXGHVKLFAKIENQQGIDNIDEIIEAADGIMIARGDMGIEVPFEMVPVYQ
KMIITKVNAAGKAVITATNMLETMTDKPRATRSEVSDVFNAVIDGTDATMLSGESANGKYPVESVRTMATIDKNAQTLLNEYGRLDSSAFPRNNKT
DVIASAVKDATHSMDIKLVVTITETGNTARAISKFRPDADILAVTFDEKVQRSLMINWGVIPVLADKPASTDDMFEVAERVALEAGFVESGDNIVI
VAGVPVGTGGTNTMRVRTVK

SEQ ID NO. 23

TTGTCTGCTATAATAGACAAAAAGGTGGTGATATTTATGTATTTAGCATTAATCGGTGATATCATTAATTCAAAACAGATACTTGA
ACGTGAAACTTTCCAACAGTCTTTTCAGCAACTAATGACCGAACTATCTGATGTATATGGTGAAGAGCTGATTTCTCCATTCACTA
TTACAGCTGGTGATGAATTTCAAGCTTTATTGAAACCATCAAAAAAGGTATTTCAAATTATTGACCATATTCAACTAGCTCTAAAA
CCTGTTAATGTAAGGTTCGGCCTCGGTACAGGAAACATTATAACATCCATCAATTCAAATGAAAGTATCGGTGCTGATGGTCCTGC
CTACTGGCATGCTCGCTCAGCTATTAATCATATACATGATAAAAATGATTATGGAACAGTTCAAGTAGCTATTTGCCTTGATGATG
AAGACCAAAACCTTGAATTAACACTAAATAGTCTCATTTCAGCTGGTGATTTTATCAAGTCAAAATGGACTACAAACCATTTTCAA
ATGCTTGAGCACTTAATACTTCAAGATAATTATCAAGAACAATTTCAACATCAAAAGTTAGCCCAACTGGAAAATATTGAACCTAG
TGCGCTGACTAAACGCCTTAAAGCAAGCGGTCTGAAGATTTACTTAAGAACGAGAACACAGGCAGCCGATCTATTAGTTAAAAGTT
GCACTCAAACTAAAGGGGGAAGCTATGATTTC

SEQ ID NO. 24

MSAIIDKKVVIFMYLALIGDIINSKQILERETFQQSFQQLMTELSDVYGEELISPFTITAGDEFQALLKPSKKVFQIIDHIQLALKPVNVRFGLGTG
NIITSINSNESIGADGPAYWHARSAINHIHDKNDYGTVQVAICLDDEDQNLELTLNSLISAGDFIKSKWTTNHFQMLEHLILQDNYQEQFQHQKLAQ
LENIEPSALTKRLKASGLKIYLRTRTQAADLLVKSCTQTKGGSYDF

SEQ ID NO. 25

ATGTTTTATACAATTGAAGAGCTGGTAGAGCAAGCTAATAGCCAACATAAGGGTAACATAGCAGAGCTCATGATCCAAACGGAAATTGAAATGACT
GGTAGAAGTCGTGAAGAAATTCGTTATATTATGTCCCGAAATCTTGAAGTCATGAAAGCTTCTGTTATTGATGGATTAACCCCTAGTAAATCAATC
AGTGGTTTAACAGGCGGTGATGCTGTCAAGATGGATCAATATTTACAATCAGGAAAAACTATTTCAGATACCACAATCCTAGCTGCCGTTAGGAAT
GCTATGGCTGTTAATGAGTTAAATGCTAAGATGGGACTGGTCTGTGCAACACCAACTGCAGGTAGTGCAGGATGTTTACCAGCTGTGATTTCTACA
GCCATTGAAAAGCTTAATTTAACAGAAGAAGAGCAACTTGATTTTCTATTTACAGCCGGCGCATTTGGTCTCGTCATTGGTAATAATGCCTCTATC
TCAGGTGCAGAAGGAGGTTGCCAAGCTGAAGTTGGGTCAGCTAGTGCTATGGCTGCGGCTGCTTTAGTTATGGCTGCTGGAGGTACTCCTTTCCAA
GCTAGCCAAGCTATAGCATTTGTTATTAAAAATATGCTTGGACTTATCTGTGACCCTGTTGCAGGTTTAGTTGAAGTCCCTTGTGTGAAGCGGAAT
GCTCTTGGATCAAGTTTTGCACTTGTTGCTGCTGATATGGCCTTGGCTGGTATTGAATCGCAAATTCCAGTAGATGAAGTTATTGATGCAATGTAT
CAAGTTGGATCAAGTTTACCGACTGCTTTTCGTGAGACTGCAGAAGGAGGACTTGCTGCCACGCCGACAGGAAGACGTTATAGTAAAGAAATTTTT
GGGGAA

SEQ ID NO. 26

MFYTIEELVEQANSQHKGNIAELMIQTEIEMTGRSREEIRYIMSRNLEVMKASVIDGLTPSKSISGLTGGDAVKMDQYLQSGKTISDTTILAAVRN
AMAVNELNAKMGLVCATPTAGSAGCLPAVISTAIEKLNLTEEEQLDFLFTAGAFGLVIGNNASISGAEGGCQAEVGSASAMAAAALVMAAGGTPFQ
ASQAIAFVIKNMLGLICDPVAGLVEVPCVKRNALGSSFALVAADMALAGIESQIPVDEVIDAMYQVGSSLPTAFRETAEGGLAATPTGRRYSKEIF
GE

SEQ ID NO. 27

ATGAGCGTATATGTTAGTGGAATAGGAATTATTTCTTCTTTGGGAAAGAATTATAGCGAGCATAAACAGCATCTCTTCGACTTAAAAGAAGGAATTT
CTAAACATTTATATAAAAATCACGACTCTATTTTAGAATCTTATACAGGAAGCATAACTAGTGACCCAGAGGTTCCTGAGCAATACAAAGATGAGAC
ACGTAATTTTAAATTTGCTTTTACCGCTTTTGAAGAGGCTCTTGCTTCTTCAGGTGTTAATTTAAAAGCTTATCATAATATTGCTGTGTGTTTAGGG
ACCTCACTTGGGGGAAAGAGTGCTGGTCAAAATGCCTTGTATCAATTTGAAGAAGGAGAGCGTCAAGTAGATGCTAGTTTATTAGAAAAAGCATCTG
TTTACCATATTGCTGATGAATTGATGGCTTATCATGATATTGTGGGAGCTTCGTATGTTATTTCAACCGCCTGTTCTGCAAGTAATAATGCCGTAAT
ATTAGGAACACAATTACTTCAAGATGGCGATTGTGATTTAGCTATTTGTGGTGGCTGTGATGAGTTAAGTGATATTTCTTTAGCAGGCTTCACATCA
CTAGGAGCTATTAATACAGAAATGGCATGTCAGCCCTATTCTTCTGGAAAAGGAATCAATTTGGGTGAGGGCGCTGGTTTTGTTGTTCTTGTCAAAG
ATCAGTCCTTAGCTAAATATGGAAAAATTATCGGTGGTCTTATTACTTCAGATGGTTATCATATAACAGCACCTAAGCCAACAGGTGAAGGGGCGGC
ACAGATTGCAAAGCAGCTAGTGACTCAAGCAGGTATTGACTACAGTGAGATTGACTATATTAACGGTCACGGTACAGGTACTCAAGCTAATGATAAA
ATGGAAAAAAATATGTATGGTAAGTTTTTCCCGACAACGACATTGATCAGCAGTACCAAGGGGCAAACGGGTCATACTCTAGGGGCTGCAGGTATTA
TCGAATTGATTAATTGTTTAGCGGCAATAGAGGAACAGACTGTACCAGCAACTAAAAATGAGATTGGGATAGAAGGTTTTCCAGAAAATTTTGTCTA
TCATCAAAAGAGAGAATACCCAATAAGAAATGCTTTAAATTTTTCGTTTGCTTTTGGTGGAAATAATAGTGGTGTCTTATTGTCATCTTTAGATTCA
CCTCTAGAAACATTACCTGCTAGAGAAAATCTTAAAATGGCTATCTTATCATCTGTTGCTTCCATTTCTAAGAATGAATCACTTTCTATAACCTATG
AAAAAGTTGCTAGTAATTTCAACGACTTTGAAGCATTACGCTTTAAAGGGGCTAGACCACCCAAAACTGTCAACCCAGCACAATTTAGGAAAATGGA
TGATTTTTCCAAAATGGTTGCCGTAACAACAGCTCAAGCACTAATAGAAAGCAATATTAATCTAAAAAAACAAGATACTTCAAAAGTAGGAATTGTA
TTTACAACACTTTCTGGACCAGTTGAGGTTGTTGAAGGTATTGAAAAGCAAATCACAACAGAAGGATATGCACATGTTTCTGCTTCACGATTCCCGT
TTACAGTAATGAATGCAGCAGCTGGTATGCTTTCTATCATTTTTAAAATAACAGGTCCTTTATCTGTCATTTCGACAAATAGTGGAGCGCTTGATGG
TATACAATATGCCAAGGAAATGATGCGTAACGATAATCTAGACTATGTGATTCTTGTTTCTGCTAATCAGTGGACAGACATGAGTTTTATGTGGTGG
CAACAATTAAACTATGATAGTCAAATGTTTGTCGGTTCTGATTATTGTTCAGCACAAGTCCTCTCTCGTCAAGCATTGGATAATTCTCCTATAATAT
TAGGTAGTAAACAATTAAAATATAGCCATAAAACATTCACAGATGTGATGACTATTTTTGATGCTGCGCTTCAAAATTTATTATCAGACTTAGGACT
AACCATAAAAGATATCAAAGGTTTCGTTTGGAATGAGCGGAAGAAGGCAGTTAGTTCAGATTATGATTTCTTAGCGAACTTGTCTGAGTATTATAAT
ATGCCAAACCTTGCTTCTGGTCAGTTTGGATTTTCATCTAATGGTGCTGGTGAAGAACTGGACTATACTGTTAATGAAAGTATAGAAAAGGGCTATT
ATTTAGTCCTATCTTATTCGATCTTCGGTGGTATCTCTTTTGCTATTATTGAAAAAAGG

SEQ ID NO. 28

MSVYVSGIGIISSLGKNYSEHKQHLFDLKEGISKHLYKNHDSILESYTGSITSDPEVPEQYKDETRNFKFAFTAFEEALASSGVNLKAYHNIAVCLG
TSLGGKSAGQNALYQFEEGERQVDASLLEKASVYHIADELMAYHDIVGASYVISTACSASNNAVILGTQLLQDGDCDLAICGGCDELSDISLAGFTS
LGAINTEMACQPYSSGKGINLGEGAGFVVLVKDQSLAKYGKIIGGLITSDGYHITAPKPTGEGAAQIAKQLVTQAGIDYSEIDYINGHGTGTQANDK
MEKNMYGKFFPTTTLISSTKGQTGHTLGAAGIIELINCLAAIEEQTVPATKNEIGIEGFPENFVYHQKREYPIRNALNFSFAFGGNNSGVLLSSLDS
PLETLPARENLKMAILSSVASISKNESLSITYEKVASNFNDFEALRFKGARPPKTVNPAQFRKMDDFSKMVAVTTAQALIESNINLKKQDTSKVGIV
FTTLSGPVEVVEGIEKQITTEGYAHVSASRFPFTVMNAAAGMLSIIFKITGPLSVISTNSGALDGIQYAKEMMRNDNLDYVILVSANQWTDMSFMWW
QQLNYDSQMFVGSDYCSAQVLSRQALDNSPIILGSKQLKYSHKTFTDVMTIFDAALQNLLSDLGLTIKDIKGFVWNERKKAVSSDYDFLANLSEYYN
MPNLASGQFGFSSNGAGEELDYTVNESIEKGYYLVLSYSIFGGISFAIIEKR

SEQ ID NO. 29

ATGAAAATAGATGACCTAAGAAAAAGCGACAATGTTGAAGATCGTCGCTCCAGTAGCGGAGGTTCATTCTCTAGCGGAGGAAGTGGATTACCGATT
CTTCAACTTTTATTGCTGCGAGGGAGTTGGAAAACCAAGCTTGTGGTTTTAATCATCTTACTGCTACTTGGCGGAGGGGGACTAACCAGCATTTTT
AATGACTCATCCTCACCTTCTAGTTACCAATCTCAGAATGTCTCACGTTCTGTTGATAATAGCGCAACGAGAGAACAAATCGATTTCGTTAATAAA
GTCCTTGGCTCAACTGAGGATTTCTGGTCACAAGAATTCCAAACCCAAGGTTTTGGAAATTATAAGGAACCAAAACTTGTTCTTTACACCAATTCA
ATTCAAACAGGTTGTGGTATAGGTGAATCTGCTTCAGGACCATTTTATTGTTCAGCAGATAAAAAAATCTATCTTGATATTTCTTTTTACAATGAA
TTATCACATAAATATGGTGCTACTGGTGATTTTGCTATGGCCTACGTCATCGCCCACGAAGTTGGTCACCACATTCAAACAGAGTTAGGCATTATG
GATAAGTATAATAGAATGCGACACGGACTTACTAAGAAAGAAGCAAATGCTTTAAATGTTCGGCTAGAACTTCAAGCAGATTATTATGCAGGGGTA
TGGGCTCACTACATCAGGGGAAAAAATCTCTTAGAACAAGGAGACTTTGAAGAGGCCATGAATGCTGCCCACGCCGTCGGAGACGATACCCTTCAG
AAAGAAACCTACGGAAAATTAGTGCCTGATAGCTTTACCCATGGAACAGCTGAACAACGCCAACGTTGGTTTAACAAAGGCTTTCAATATGGTGAC
ATCCAACACGGTGATACTTTCTCCGTAGAACATCTA

SEQ ID NO. 30

MKIDDLRKSDNVEDRRSSSGGSFSSGGSGLPILQLLLLRGSWKTKLVVLIILLLLGGGGLTSIFNDSSSPSSYQSQNVSRSVDNSATREQIDFVNK
VLGSTEDFWSQEFQTQGFGNYKEPKLVLYTNSIQTGCGIGESASGPFYCSADKKIYLDISFYNELSHKYGATGDFAMAYVIAHEVGHHIQTELGIM
DKYNRMRHGLTKKEANALNVRLELQADYYAGVWAHYIRGKNLLEQGDFEEAMNAAHAVGDDTLQKETYGKLVPDSFTHGTAEQRQRWFNKGFQYGD
IQHGDTFSVEHL

SEQ ID NO. 31

ATGAAAAGATTACATAAACTGTTTATAACCGTAATTGCTACATTAGGTATGTTGGGGGTAATGACCTTTGGTCTTCCAACGCAGCCGCAAAACGTA
ACGCCGATAGTACATGCTGATGTCAATTCATCTGTTGATACGAGCCAGGAATTTCAAAATAATTTAAAAAATGCTATTGGTAACCTACCATTTCAA
TATGTTAATGGTATTTATGAATTAAATAATAATCAGACAAATTTAAATGCTGATGTCAATGTTAAAGCGTATGTTCAAAATACAATTGACAATCAA
CAAAGACTATCAACTGCTAATGCAATGCTTGATAGAACCATTCGTCAATATCAAAATCGCAGAGATACCACTCTTCCCGATGCAAATTGGAAACCA
TTAGGTTGGCATCAAGTAGCTACTAATGACCATTATGGACATGCAGTCGACAAGGGGCATTTAATTGCCTATGCTTTAGCTGGAAATTTCAAAGGT
TGGGATGCTTCCGTGTCAAATCCTCAAAATGTTGTCACACAAACAGCTCATTCCAACCAATCAAATCAAAAAATCAATCGTGGACAAAATTATTAT
GAAAGCTTAGTTCGTAAGGCGGTTGACCAAAACAAACGTGTTCGTTACCGTGTAACTCCATTGTACCGTAATGATACTGATTTAGTTCCATTTGCA
ATGCACCTAGAAGCTAAATCACAAGATGGCACATTAGAATTTAATGTTGCTATTCCAAACACACAAGCATCATACACTATGGATTATGCAACAGGA
GAAATAACACTAAAT

SEQ ID NO. 32

MKRLHKLFITVIATLGMLGVMTFGLPTQPQNVTPIVHADVNSSVDTSQEFQNNLKNAIGNLPFQYVNGIYELNNNQTNLNADVNVKAYVQNTIDNQ
QRLSTANAMLDRTIRQYQNRRDTTLPDANWKPLGWHQVATNDHYGHAVDKGHLIAYALAGNFKGWDASVSNPQNVVTQTAHSNQSNQKINRGQNYY
ESLVRKAVDQNKRVRYRVTPLYRNDTDLVPFAMHLEAKSQDGTLEFNVAIPNTQASYTMDYATGEITLN

SEQ ID NO. 33

ATGAGTAAACGACAAAATTTAGGAATTAGTAAAAAAGGAGCAATTATATCAGGGCTCTCAGTGGCACTAATTGTAGTAATAGGTGGCTTTTTATGG
GTACAATCTCAACCTAATAAGAGTGCAGTAAAAACTAACTACAAAGTTTTTAATGTTAGAGAAGGAAGTGTTTCGTCCTCAACTCTTTTGACAGGA
AAAGCTAAGGCTAATCAAGAACAGTATGTGTATTTTGATGCTAATAAAGGTAATCGAGCAACTGTCACAGTTAAAGTGGGTGATAAAATCACAGCT
GGTCAGCAGTTAGTTCAATATGATACAACAACTGCACAAGCAGCCTACGACACTGCTAATCGTCAATTAAATAAAGTAGCGCGTCAGATTAATAAT
CTAAAGACAACAGGAAGTCTTCCAGCTATGGAATCAAGTGATCAATCTTCTTCATCATCACAAGGACAAGGGACTCAATCGACTAGTGGTGCGACG
AATCGTCTACAGCAAAATTATCAAAGTCAAGCTAATGCTTCATACAACCAACAACTTCAAGATTTGAATGATGCTTATGCAGATGCACAGGCAGAA
GTAAATAAAGCACAAAAAGCATTGAATGATACTGTTATTACAAGTGACGTATCAGGGACAGTTGTTGAAGTTAATAGTGATATTGATCCAGCTTCA
AAAACTAGTCAAGTACTTGTCCATGTAGCAACTGAAGGTAAACTCCAAGTACAAGGAACGATGAGTGAGTATGATTTGGCTAATGTTAAAAAAGAC
CAGGCTGTTAAAATAAAATCTAAGGTCTATCCTGACAAGGAATGGGAAGGTAAAATTTCATATATCTCAAATTATCCAGAAGCAGAAGCAAACAAC
AATGACTCTAATAACGGCTCTAGTGCTGTAAATTATAAATATAAAGTAGATATTACTAGCCCTCTCGATGCATTAAAACAAGGTTTTACCGTATCA
GTTGAAGTAGTTAATGGAGATAAGCACCTTATTGTCCCTACAAGTTCTGTGATAAACAAAGATAATAAACACTTTGTTTGGGTATACAATGATTCT
AATCGTAAAATTTCCAAAGTTGAAGTCAAAATTGGTAAAGCTGATGCTAAGACACAAGAAATTTTATCAGGTTTGAAAGCAGGACAAATCGTGGTT
ACTAATCCAAGTAAAACCTTCAAGGATGGGCAAAAAATTGATAATATTGAATCAATCGATCTTAACTCTAATAAGAAATCAGAGGTGAAA

SEQ ID NO. 34

MSKRQNLGISKKGAIISGLSVALIVVIGGFLWVQSQPNKSAVKTNYKVFNVREGSVSSSTLLTGKAKANQEQYVYFDANKGNRATVTVKVGDKITAG
QQLVQYDTTTAQAAYDTANRQLNKVARQINNLKTTGSLPAMESSDQSSSSSQGQGTQSTSGATNRLQQNYQSQANASYNQQLQDLNDAYADAQAEVN
KAQKALNDTVITSDVSGTVVEVNSDIDPASKTSQVLVHVATEGKLQVQGTMSEYDLANVKKDQAVKIKSKVYPDKEWEGKISYISNYPEAEANNNDS
NNGSSAVNYKYKVDITSPLDALKQGFTVSVEVVNGDKHLIVPTSSVINKDNKHFVWVYNDSNRKISKVEVKIGKADAKTQEILSGLKAGQIVVTNPS
KTFKDGQKIDNIESIDLNSNKKSEVK

SEQ ID NO. 35

ATGAAAAAAATTGGAATTATTGTCCTCACACTACTGACCTTCTTTTTGGTATCTTGCGGACAACAAACTAAACAAGAAAGCACTAAAACAACTATT
TCTAAAATGCCTAAAATTGAAGGCTTCACCTATTATGGAAAAATTCCTGAAAATCCGAAAAAAGTAATTAATTTTACATATTCTTACACTGGGTAT
TTATTAAAACTAGGTGTTAATGTTTCAAGTTACAGTTTAGACTTAGAAAAAGATAGCCCCGTTTTTGGTAAACAACTGAAAGAAGCTAAAAAATTA
ACTGCTGATGATACAGAAGCTATTGCCGCACAAAAACCTGATTTAATCATGGTTTTCGATCAAGATCCAAACATCAATACTCTGAAAAAAATTGCA
CCAACTTTAGTTATTAAATATGGTGCACAAAATTATTTAGATATGATGCCAGCCTTGGGGAAAGTATTCGGTAAAGAAAAAGAAGCTAATCAGTGG
GTTAGCCAATGGAAAACTAAAACTCTCGCTGTCAAAAAAGATTTACACCATATCTTAAAGCCTAACACTACTTTTACTATTATGGATTTTTATGAT
AAAAATATCTATTTATATGGTAATAATTTTGGACGCGGTGGAGAACTAATCTATGATTCACTAGGTTATGCTGCCCCAGAAAAAGTCAAAAAAGAT
GTCTTTAAAAAAGGGTGGTTTACCGTTTCGCAAGAAGCAATCGGTGATTACGTTGGAGATTATGCCCTTGTTAATATAAACAAAACGACTAAAAAA
GCAGCTTCATCACTTAAAGAAAGTGATGTCTGGAAGAATTTACCAGCTGTCAAAAAAGGGCACATCATAGAAAGTAACTACGACGTGTTTTATTTC
TCTGACCCTCTATCTTTAGAAGCTCAATTAAAATCATTTACAAAGGCTATCAAAGAAAATACAAAT

SEQ ID NO. 36

MKKIGIIVLTLLTFFLVSCGQQTKQESTKTTISKMPKIEGFTYYGKIPENPKKVINFTYSYTGYLLKLGVNVSSYSLDLEKDSPVF
GKQLKEAKKLTADDTEAIAAQKPDLIMVFDQDPNINTLKKIAPTLVIKYGAQNYLDMMPALGKVFGKEKEANQWVSQWKTKTLAVK
KDLHHILKPNTTFTIMDFYDKNIYLYGNNFGRGGELIYDSLGYAAPEKVKKDVFKKGWFTVSQEAIGDYVGDYALVNINKTTKKAA
SSLKESDVWKNLPAVKKGHIIESNYDVFYFSDPLSLEAQLKSFTKAIKENTN

SEQ ID NO. 37

ATGAAAGTGAAAAATAAGATTTTAACGATGGTAGCACTTACTGTCTTAACATGTGCTACTTATTCATCAATCGGTTATGCTGATACAAGTGATAAGA
ATACTGACACGAGTGTCGTGACTACGACCTTATCTGAGGAGAAAAGATCAGATGAACTAGACCAGTCTAGTACTGGTTCTTCTTCTGAAAATGAATC
GAGTTCATCAAGTGAACCAGAAACAAATCCGTCAACTAATCCACCTACAACAGAACCATCGCAACCCTCACCTAGTGAAGAGAACAAGCCTGATGGT
AGAACGAAGACAGAAATTGGCAATAATAAGGATATTTCTAGTGGAACAAAAGTATTAATTTCAGAAGATAGTATTAAGAATTTTAGTAAAGCAAGTA
GTGATCAAGAAGAAGTGGATCGCGATGAATCATCATCTTCAAAAGCAAATGATGGGAAAAAAGGCCACAGTAAGCCTAAAAAGGAACTTCCTAAAAC
AGGAGATAGCCACTCAGATACTGTAATAGCATCTACGGGAGGGATTATTCTGTTATCATTAAGTTTTTACAATAAGAAAATGAAACTTTAT

SEQ ID NO. 38

MKVKNKILTMVALTVLTCATYSSIGYADTSDKNTDTSVVTTTLSEEKRSDELDQSSTGSSSENESSSSSEPETNPSTNPPTTEPSQPSPSEENKPDG
RTKTEIGNNKDISSGTKVLISEDSIKNFSKASSDQEEVDRDESSSSKANDGKKGHSKPKKELPKTGDSHSDTVIASTGGIILLSLSFYNKKMKLY

SEQ ID NO. 39

ATGAAAAGGATACGGAAAAGCCTTATTTTTGTTCTCGGAGTAGTTACCCTAATTTGCTTATGTGCTTGTACTAAACAAAGCCAGCAAAAAAATGGCT
TGTCAGTAGTGACTAGCTTTTATCCAGTATATTCCATTACAAAAGCAGTTTCTGGTGATTTGAATGATATTAAAATGATTCGATCACAGTCAGGTAT
TCATGGTTTTGAACCCTCATCAAGTGATGTTGCTGCCATTTATGATGCTGATCTATTTCTTTATCATTCGCACACACTAGAAGCTTGGGCGAGACGT
TTGGAACCTAGTTTGCATCACTCTAAAGTATCTGTAATTGAAGCTTCAAAAGGTATGACTTTGGATAAAGTTCATGGCTTAGAAGATGTAGAGGCAG
AAAAAGGAGTAGATGAGTCAACCTTGTATGACCCTCACACTTGGAATGACCCTGTAAAAGTATCTGAGGAAGCACAACTCATCGCTACACAATTAGC
TAAAAAGGATCCTAAAAACGCTAAGGTTTATCAAAAAAATGCTGATCAATTTAGTGACAAGGCAATGGCTATTGCAGAGAAGTATAAGCCAAAATTT
AAAGCTGCAAAGTCTAAATACTTTGTGACTTCACATACAGCATTCTCATACTTAGCTAAGCGATACGGATTGACTCAGTTAGGTATTGCAGGTGTCT
CAACCGAGCAAGAACCTAGTGCTAAAAAATTAGCCGAAATTCAGGAGTTTGTGAAAACATATAAGGTTAAGACTATTTTTGTTGAAGAAGGAGTCTC
ACCTAAATTAGCTCAAGCAGTAGCTTCAGCTACTCGAGTTAAAATTGCAAGTTTAAGTCCTTTARAAGCAGTTCCCAAAAACAATAAAGATTACTTA
GAAAATTTGGAAACTAATCTTAAGGTACTTGTCAAATCGTTAAATCAATAG

SEQ ID NO. 40

MKRIRKSLIFVLGVVTLICLCACTKQSQQKNGLSVVTSFYPVYSITKAVSGDLNDIKMIRSQSGIHGFEPSSSDVAAIYDADLFLYHSHTLEAWARR
LEPSLHHSKVSVIEASKGMTLDKVHGLEDVEAEKGVDESTLYDPHTWNDPVKVSEEAQLIATQLAKKDPKNAKVYQKNADQFSDKAMAIAEKYKPKF
KAAKSKYFVTSHTAFSYLAKRYGLTQLGIAGVSTEQEPSAKKLAEIQEFVKTYKVKTIFVEEGVSPKLAQAVASATRVKIASLSPLXAVPKNNKDYL
ENLETNLKVLVKSLNQ

SEQ ID NO. 41

ATGCCTAAGAAGAAATCAGATACCCCAGAAAAAGAAGAAGTTGTCTTAACGGAATGGCAAAAGCGTAACCTTGAATTTTTAAAAAAACGCAAAGAAG
ATGAAGAAGAACAAAAACGTATTAACGAAAAATTACGCTTAGATAAAAGAAGTAAATTAAATATTTCTTCTCCTGAAGAACCTCAAAATACTACTAA
AATTAAGAAGCTTCATTTTCCAAAGATTTCAAGACCTAAGATTGAAAAGAAACAGAAAAAAGAAAAAATAGTCAACAGCTTAGCCAAAACTAATCGC
ATTAGAACTGCACCTATATTTGTAGTAGCATTCCTAGTCATTTTAGTTTCCGTTTTCCTACTAACTCCTTTTAGTAAGCAAAAAACAATAACAGTTA
GTGGAAATCAGCATACACCTGATGATATTTTGATAGAGAAAACGAATATTCAAAAAAACGATTATTTCTTTTCTTTAATTTTTAAACATAAAGCTAT
TGAACAACGTTTAGCTGCAGAAGATGTATGGGTAAAAACAGCTCAGATGACTTATCAATTTCCCAATAAGTTTCATATTCAAGTTCAAGAAAATAAG

ATTATTGCATATGCACATACAAAGCAAGGATATCAACCTGTCTTGGAAACTGGAAAAAAGGCTGATCCTGTAAATAGTTCAGAGCTACCAAAGCACT
TCTTAACAATTAACCTTGATAAGGAAGATAGTATTAAGCTATTAATTAAAGATTTAAAGGCTTTAGACCCTGATTTAATAAGTGAGATTCAGGTGAT
AAGTTTAGCTGATTCTAAAACGACACCTGACCTCCTGCTGTTAGATATGCACGATGGAAATAGTATTAGAATACCATTATCTAAATTTAAAGAAAGA
CTTCCTTTTTACAAACAAATTAAGAAGAACCTTAAGGAACCTTCTATTGTTGATATGGAAGTGGGAGTTTACACAACAACAAATACCATTGAATCAA
CCCCTGTTAAAGCAGAAGATACAAAAAATAAATCAACTGATAAAACACAAACACAAAATGGTCAGGTTGCGGAAAATAGTCAAGGACAAACAAATAA
CTCAAATACTAATCAACAAGGACAACAGATAGCAACAGAGCAGGCACCTAACCCTCAAAATGTTAAT

SEQ ID NO. 42

MPKKKSDTPEKEEVVLTEWQKRNLEFLKKRKEDEEEQKRINEKLRLDKRSKLNISSPEEPQNTTKIKKLHFPKISRPKIEKKQKKEKIVNSLAKTNR
IRTAPIFVVAFLVILVSVFLLTPFSKQKTITVSGNQHTPDDILIEKTNIQKNDYFFSLIFKHKAIEQRLAAEDVWVKTAQMTYQFPNKFHIQVQENK
IIAYAHTKQGYQPVLETGKKADPVNSSELPKHFLTINLDKEDSIKLLIKDLKALDPDLISEIQVISLADSKTTPDLLLLDMHDGNSIRIPLSKFKER
LPFYKQIKKNLKEPSIVDMEVGVYTTTNTIESTPVKAEDTKNKSTDKTQTQNGQVAENSQGQTNNSNTNQQGQQIATEQAPNPQNVN

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 May 2004 (21.05.2004)

PCT

(10) International Publication Number
WO 2004/041157 A3

(51) International Patent Classification[7]: A61K 39/385, 39/02, 39/09, 39/00

(21) International Application Number: PCT/US2003/029167

(22) International Filing Date: 15 September 2003 (15.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/410,839 13 September 2002 (13.09.2002) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/410,839 (CIP)
Filed on 13 September 2002 (13.09.2002)

(71) Applicant (*for all designated States except US*): **CHIRON CORPORATION** [US/US]; 4560 Horton Street, Emeryville, CA 94608-2916 (US).

(72) Inventor; and
(75) Inventor/Applicant (*for US only*): **RAPPUOLI, Rino** [IT/IT]; Chiron Corporation, P.O. Box 8097, Emeryville, CA 94662-8097 (US).

(74) Agents: **HALE, Rebecca, M.** et al.; Chiron Corporation, Intellectual Property-R338, P.O. Box 8097, Emeryville, CA 94662-8097 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report: 16 September 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/041157 A3

(54) Title: GROUP B STREPTOCOCCUS VACCINE

(57) Abstract: This application relates to improved Group B Streptococcus ("GBS") saccharide-based vaccines comprising combinations of GBS polysaccharides with polypeptide antigens, and *vice versa*, such that the polypeptide and the saccharide each contribute to the immunological response in a recipient. The combination is particularly advantageous where the saccharide and polypeptide are from different GBS serotypes. The combined antigens may be present as a simple combination where separate saccharide and polypeptide antigens are administered together, or they may be present as a conjugated combination, where the saccharide and polypeptide antigens are covalently linked to each other. Preferably, the immunogenic compositions of the invention comprise a GBS saccharide antigen and at least two GBS polypeptide antigens, wherein said GBS saccharide antigen comprises a saccharide selected form GBS serotype Ia, Ib, and III, and wherein said GBS polypeptide antigens comprise a combination of at least two polypeptide or fragments thereof selected from the antigen group consisting of GBS 80, GBS 91, GBS 104, GBS 147, GBS 173, GBS 276, GBS 305, GBS 313, GBS 322, GBS 328, GBS 330, GBS 338, GBS 358, GBS 361, GBS 404, GBS 656, GBS 690, and GBS 691.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/29167

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 39/385, 39/02, 39/09, 39/00
US CL : 424/197.11, 234.1, 244.1, 184.1, 236.1, 831
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/197.11, 234.1, 244.1, 184.1, 236.1, 831

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/34771 A2 (CHIRON S.P.A.) 02 May 2002 (02.05.2002), pages 7, 841 and 842.	1-17
Y	US 6,372,222 B1 (MICHON et al) 16 April 2002 (16.04.2002), claims and Examples.	1-17
Y	US 6,426,074 B1 (MICHEL et al.) 30 July 2002 (30.06.2002), Example 14.	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
15 April 2004 (15.04.2004)

Date of mailing of the international search report
02 AUG 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer
S. Devi, Ph.D.
Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/29167

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:
GBS saccharide antigen species: serotype Ia; serotype Ib; and serotype III.

The claims are deemed to correspond to the species listed above in the following manner:
Claims 1 and 17.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The saccharide antigen species listed above do not share significant structural elements and immunogenici specificity.

Continuation of B. FIELDS SEARCHED Item 3:
DIALOG, WEST, EMBASE, BIOSIS, MEDLINE
GBS or group B streptococc?, (Ia or Ib or III), GBS79, GBS80 to GBS 691, inventor's name